Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Vanderver A, Adang L, Gavazzi F, et al. Janus kinase inhibition in the Aicardi–Goutières syndrome. N Engl J Med 2020;383:986-9. DOI: 10.1056/NEJMc2001362

Table of contents for protocols associated with 20-01362 - Janus kinase inhibition in Aicardi Goutières Syndrome

"Compassionate Use Treatment Protocol I4V-MC-JAGA: Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis"

This protocol was originally approved by the IRB at the Children's National Medical Center in February 2016. This natural protocol was transferred in the fall of 2016 to the Children's Hospital of Philadelphia. It should be noted that several versions of this protocol were approved by Lilly before the study was implemented for individuals with Aicardi Goutieres Syndrome. For the purposes of review of this study, the protocol that was in place when the first patients in this report were started on baricitinib, approved at Children's National, is included as the "first" version of this protocol, although additional versions of this protocol are available upon request.

"Statistical Analysis Plan: Compassionate Use Treatment I4V-MC-JAGA: Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis"

This statistical analysis plan was originally approved by the sponsor in April 2016. The analysis plan for the AGS neurologic outcomes was added after enrollment began, and the protocol was approved by the sponsor in October 2019.

“The Myelin Disorders Biorepository Project and Global Leukodystrophy Initiative Clinical Trials Network” at the Children’s Hospital of Philadelphia

This protocol was originally submitted to the IRB at the Children’s National Medical Center ~ 2003. The earliest electronic version of this protocol is from 2005. This natural history protocol has continued to evolve and was transferred in the fall of 2016 to the Children’s Hospital of Philadelphia. For the purposes of review of this study, the protocol that was in place when the first patients in this report were started on baricitinib, approved in November 2015, is included as the “first” version of this protocol, although additional versions of this protocol between 2005-2016 are available upon request.

Changes to "Compassionate Use Treatment Protocol I4V-MC-JAGA: Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis" at the Children's Hospital of Philadelphia

This protocol was originally approved by the IRB at the Children's National Medical Center in February 2016. This natural protocol was transferred in the fall of 2016 to the Children's Hospital of Philadelphia. It should be noted that several versions of this protocol were approved by Lilly before the study was implemented for individuals with Aicardi Goutieres Syndrome. For the purposes of review of this study, the protocol that was in place when the first patients in this report were started on baricitinib, approved at Children's National, is included as the "first" version of this protocol, although additional versions of this protocol are available upon request.

All other amendments were personnel amendments that did not modify the protocol.

Date	Protocol	Comments
2/13/2020	I4V-MC-JAGA AMD28	This amendment involves updates to the Baricitinib Investigator's Brochure and risk profile and adding PK testing to the study procedures. The consent was updated to incorporate these changes. Additional edits were made to the consent to align with the consent form of another similar study (CHOP IRB Study #15414).
8/12/2019	I4V-MC-JAGA AMD24	This amendment involves an updated investigator's brochure for baricitinib.
1/14/2019	I4V-MC-JAGA AMD20	This amendment involves revising the risks associated with baricitinib. The consent document has been correspondingly updated.
10/31/2018	I4V-MC-JAGA AMD17	This amendment includes modifications to the investigator's brochure for baricitinib.
8/31/2018	I4V-MC-JAGA AMD16	This amendment involves revising the protocol and AGS protocol addendum to increase the total enrollment goal from 75 subjects to 85 subjects (the CHOP enrollment goal remains unchanged at 50 subjects). The consent form was edited accordingly. A CHOP specific protocol addendum has been submitted to reflect that Visit 2 laboratory assessments may be omitted for very young, small children for whom blood volume is a consideration, providing that Visit 2 is within approximately one week of screening labs (Visit 1).
8/7/2018	I4V-MC-JAGA AMD15	This amendment involves edits to the consent form to inform subjects that baricitnib has been FDA approved for treatment of moderate to severe rheumatoid arthritis in adults, but is not approved for use in children, increasing the enrollment goal at CHOP to 50 subjects, and updating the application to reflect that legally authorized representatives can consent for adults with diminished capacity.
6/25/2018	I4V-MC-JAGA AMD14	This amendment involves broadening the inclusion criteria to allow enrollment of AGS subjects less than 17.5 months old. A protocol addendum with special considerations for subjects less than 6 months of age was provided. This includes instructions on dosing, vaccinations, kidney function, and blood draws. These changes do not affect the IRB's previous risk-benefit assessment of the study.
3/23/2018	I4V-MC-JAGA AMD9	This amendment involves revising the protocol to allow for study drug tablet splitting on a case- by-case basis with sponsor approval. Additional changes (which primarily do not affect CHOP subjects with AGS) include broadening the inclusion criteria, clarifying and revising the objectives for juvenile dermatomyositis (JDM), clarifying urine assessments, and clarifying the statistical analysis plan. Amendment (t) Electronically Signed and Approved by Lilly: 14 February 2018
12/14/2017	I4V-MC-JAGA AMD8	This amendment includes revising the consent form to include information on possible risks associated with the study drug (pulmonary emboli and cardiac monitoring) as requested by the IRB as part of RE12

		and providing an updated Investigator's Brochure. In addition, adults with diminished capacity will now be eligible for study participation at CHOP.
8/23/2017	I4V-MC-JAGA AMD5	This amendment includes an updated Investigator's Brochure which identifies new risks. The consent form has been modified to incorporate the updated risk information.
5/30/2017	I4V-MC-JAGA AMD4	This amendment includes the submission of an Arabic-translated consent form.
2/21/2017	I4V-MC-JAGA AMD1	This amendment includes changes to the dosing regimen of the drug, minor additions/clarifications of study procedures, addition of an optional washout period of 4 weeks, and increase in study-wide study enrollment from 35 to 60 subjects. Non-substantial updates have been made to the investigator's brochure for baricitinib.
1/11/2017	I4V-MC-JAGA Approval of Initial Submission at CHOP	Amendment (s) Electronically Signed and Approved by Lilly: 23 September 2016 was the protocol that was implemented
FEB 2016	I4V-MC-JAGA Approval of Initial Submission at Children’s National	Amendment (r) Electronically Signed and Approved by Lilly: 20 February 2015 was the protocol that was implemented

1. Compassionate Use Treatment Protocol I4V-MC-JAGA(u): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Confidential Information

Baricitinib (LY3009104)

Study I4V-MC-JAGA is an open-label compassionate use treatment program to provide baricitinib to patients with conditions expected to benefit from JAK inhibition: CANDLE, CANDLE-related conditions, SAVI, and severe juvenile dermatomyositis. Patients will receive an initial dose based on their weight class and eGFR that may be escalated to determine a tolerable dose. Patients may be dosed for up to 288 weeks. It is anticipated that up to 85 patients may be treated with baricitinib in an individualized manner. The treatment guidelines contained herein are for compassionate use only. Within these guidelines, open-label baricitinib will only be administered to patients who meet inclusion and exclusion criteria.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly: 14 October 2011.
Approval dates for Amendments (a) through (t) are shown on the following page.
Amendment (u) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 08-Aug-2018 GMT

Amendment (a) Electronically Signed and Approved by Lilly: 20 October 2011.
Amendment (b) Electronically Signed and Approved by Lilly: 15 December 2011.
Amendment (c) Electronically Signed and Approved by Lilly: 17 January 2012.
Amendment (d) Electronically Signed and Approved by Lilly: 21 February 2012.
Amendment (e) Electronically Signed and Approved by Lilly: 24 March 2012.
Amendment (f) Electronically Signed and Approved by Lilly: 08 May 2012.
Amendment (g) Electronically Signed and Approved by Lilly: 24 August 2012.
Amendment (h) Electronically Signed and Approved by Lilly: 08 September 2012.
Amendment (i) Electronically Signed and Approved by Lilly: 05 March 2013.
Amendment (j) Electronically Signed and Approved by Lilly: 03 April 2013.
Amendment (k) Electronically Signed and Approved by Lilly: 21 May 2013.
Amendment (l) Electronically Signed and Approved by Lilly: 06 August 2013.
Amendment (m) Electronically Signed and Approved by Lilly: 10 October 2013.
Amendment (n) Electronically Signed and Approved by Lilly: 05 November 2013
Amendment (o) Electronically Signed and Approved by Lilly: 09 December 2013.
Amendment (p) Electronically Signed and Approved by Lilly: 30 January 2014.
Amendment (q) Electronically Signed and Approved by Lilly: 09 May 2014.
Amendment (r) Electronically Signed and Approved by Lilly: 20 February 2015
Amendment (s) Electronically Signed and Approved by Lilly: 23 September 2016
Amendment (t) Electronically Signed and Approved by Lilly: 14 February 2018

2. Synopsis

I4V-MC-JAGA (JAGA) is an open-label compassionate use study. Patients who weigh at least 8.5 kg and who are at least 17.5 months of age are eligible to enter this study (patients who weigh less than 8.5 kg or are younger than 17.5 months may be considered for enrollment after discussion with the Sponsor). Throughout the study, the patient's disease severity will be recorded on a daily diary by the patient or patient's parent or legal guardian. Average diary scores and ongoing active clinical disease will define inadequate response to therapy and will be used to trigger changes in daily doses of baricitinib. Once a patient achieves a low average daily diary score (defined below), the investigator will begin to taper the patient's steroid dose (if the patient is receiving steroids). Patients whose average diary score decreases substantially, but who do not meet the threshold for adequate response/steroid weaning may continue in the study, if the investigator and Sponsor agree that the patient has shown favorable response to treatment with baricitinib, and that it is in the best interest of the patient to continue treatment.

Synopsis: Study I4V-MC-JAGA

Name of Investigational Product: Baricitinib	
Title of Study: Compassionate Use Treatment Protocol I4V-MC-JAGA: Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis	
Number of Planned Patients/Subjects: Entered: up to 85 Enrolled: up to 85 Completed: up to 85	**Phase of Development:** Not Applicable for Compassionate Use
Length of Study: Up to 292 weeks Planned first patient visit: Nov 2011	
Objectives: The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, juvenile dermatomyositis (JDM), or SAVI results in a reduction in the patient's mean daily diary scores as follows: • CANDLE diary: reduction in mean daily score to <0.5 • SAVI diary: reduction in mean daily score to <1.0, exclusive of respiratory/breathing symptom, and a <1.0 increase from baseline in the respiratory/breathing symptom • JDM diary: reduction in mean daily score exclusive of fever and headache symptoms by ≥0.25	
Study Design: An open-label, compassionate use treatment protocol. Patients will be treated for a maximum of 288 weeks followed by an optional 4 week washout period to monitor safety post treatment	
Diagnosis and Main Criteria for Inclusion and Exclusions: Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder for which there is reason to believe that JAK 1/2 inhibition will be beneficial. One such autoinflammatory disorder is chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. CANDLE syndrome typically presents early in infancy with attacks of fever, panniculitis, arthritis, myositis, lipodystrophy, cytopenias, dyslipidemia, growth retardation, and variable elevation of acute-phase reactants. Other patients eligible to be enrolled into this study include those diagnosed with conditions related to CANDLE syndrome involving immune dysregulation: stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), an autoinflammatory syndrome with interferon (IFN) pathway dysregulation, and juvenile dermatomyositis (JDM).	
Investigational Product, Dosage, and Mode of Administration or Intervention: Baricitinib given orally according to the dosing tables.	
Planned Duration of Treatment: Patients may be treated up to 288 weeks.	
Reference Therapy, Dose, and Mode of Administration or Comparative Intervention: Not applicable	
Criteria for Evaluation: Pharmacokinetics/Pharmacodynamics: Plasma samples will be obtained at specified time points. Concentrations of baricitinib will be determined by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method.	
Statistical Methods: 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. However, 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.	

3. Table of Contents

Compassionate Use Treatment Protocol I4V-MC-JAGA(u) Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, and Severe Juvenile Dermatomyositis

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4. Abbreviations and Definitions

Term	Definition
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and 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.
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 institutional review boards [IRBs]).
AST	aspartate aminotransferase
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BID	Twice daily (divided dose two times per 24 hours)
CANDLE	chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS	cryopyrin-associated periodic syndromes
cGAMP	cyclic guanosine monophosphate- adenosine monophosphate
clinical research physician (CRP)	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
compassionate use	Compassionate use programs provide investigational products to patients for the treatment of a serious or immediately life-threatening disease or condition when there is no comparable or satisfactory alternative therapy available. They may also be referred to as expanded access programs.
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.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
DEG	differentially expressed gene
ECG	electrocardiogram

Electronic case report form (eCRF)	Sometimes referred to as clinical report form. A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
effectiveness	Effectiveness is the measure of the produced effect of an intervention when carried out in a clinical environment.
eGFR	estimated glomerular filtration rate
end of the study	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.
enrollment	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
HBV	hepatitis B virus
HIV	human immunodeficiency virus
i-proteasome	immunoproteasome complex
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
IFN	interferon
IL	interleukin
institutional review board/ethical review board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
IP-10/CXCL10	interferon inducible protein 10/ C-X-C motif chemokine 10
IVIg	intravenous immune globulin
JAGA	I4V-MC-JAGA
JAK	Janus kinase
JDM	juvenile dermatomyositis
JMP	joint contractures, muscle atrophy, and panniculitis
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.

NOMID	neonatal-onset multisystem inflammatory disease
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PK	pharmacokinetic
PPD	purified protein derivative
Ps	psoriasis
PSMB8	proteasome subunit beta type-8
QD	once daily
QID	four times daily (divided dose four times per 24 hours)
RA	rheumatoid arthritis
requesting physician	A physician who has been granted access to investigational product on a compassionate use (or expanded access) basis as a result of an unsolicited request directed to the study sponsor. The requesting physician is responsible for the conduct of a compassionate use study at a study site. If a study is conducted by a team of individuals at a study site, the requesting physician is the responsible leader of the team. Within this protocol, the requesting physician may also be referred to as principal investigator or investigator.
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. In this study, screening involves diagnostic procedures and/or tests (for example, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
STAT	signal transducers and activators of transcription
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TID	Three times daily (divided dose three times per 24 hours)
TNF	tumor necrosis factor
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal

VAS	visual analog scale
WBC	white blood cell

Compassionate Use Treatment Protocol I4V-MC-JAGA(u) Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

5. Introduction

The purpose of this open-label, compassionate use, treatment protocol is to provide baricitinib to patients with CANDLE*, CANDLE-related conditions, SAVI,* and severe juvenile dermatomyositis (JDM) who are not responsive to biologic therapies and who require treatment with high doses of steroids to control systemic signs and symptoms of their condition (or, in the opinion of the investigator, have failed an adequate course of steroids or are not suitable candidates for steroid treatment, such as patients with a confirmed genetic diagnosis of CANDLE or SAVI) and are eligible for treatment under this protocol. Baricitinib is an orally administered inhibitor of Janus kinases 1 and 2 (JAK1 and JAK2).

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 active transcription factors and 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 interferons (IFNs), interleukin (IL)-2, IL-6, IL-12, IL-23, 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 (Ps) (Boy et al. 2009; Kremer et al. 2009).

Baricitinib is being investigated for the treatment of inflammatory diseases, including RA and Ps. 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 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 single 5-mg doses to subjects with end stage renal disease. In patients with RA, baricitinib has also been administered at doses of 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.

* CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
SAVI = stimulator of interferon genes (STING)-associated vasculopathy with onset during infancy

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 infections and infestations system/organ class. 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 et al. 2006; Henderson et al. 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 et al. 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 (i.e. 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 IL-1. 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 (NOMID). Most of these diseases include fever, urticaria-like rash, and arthralgia, and are associated with gain of function mutations in the inflammasome, including, but not limited to, mutations in the NLRP3 gene (McGonagle et al. 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 [Kineret®; Biovitrum]) 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 (Arcalyst®; Regeneron) (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 mutations in the proteasome subunit beta type-8 (PSMB8) gene encoding the beta5i 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 gamma IFN, 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 (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) (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 patients do not respond to DMARDs, IL-1 or IL-6 blocking agents or 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). A review of mortality of all reported patients and those seen at the NIH suggests a mortality of more than 20% before the age of 30 (Kim H et al. in press)

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 described 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. Another patient harbors a *de novo* mutation at position c.442G>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 wildtype. 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 tumor necrosis factor (TNF). The clinical phenotype and the increased IFN response gene expression in the peripheral blood suggest a gain of function resulting 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).

- **CANDLE-Related Conditions.** A group of conditions that have very strong IFN response signature have recently been identified in the gene expression studies from whole blood. These conditions share clinical, pathological, and immunological features, which are different from those typically observed in IL-1-mediated autoinflammatory diseases (including NOMID, deficiency of IL-1 receptor antagonist, hyperimmunoglobulin D with periodic fever syndrome, TNF receptor-associated periodic syndrome, and familial Mediterranean fever) that respond to IL-1 inhibition. Many of the IFN-mediated autoinflammatory diseases do not respond to IL-1 blockade and share a clinical phenotype that may include CNS manifestations (CSF pleocytosis, aseptic meningitis, white matter disease, and basal ganglia calcifications), vasculopathy (arterial hypertension, pulmonary hypertension, vascular calcifications or livedo reticularis), metabolic changes (lipodystrophy, dyslipidemia, insulin resistance, or intra-abdominal fat deposition), musculoskeletal manifestations (myositis, arthralgias or arthritis, and/or panniculitis) and hematological manifestations (i.e. cytopenias). In these conditions, histologic features of immature neutrophils in the inflammatory infiltrate are commonly seen on skin biopsy (Canna and Goldbach-Mansky 2015).

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.

Conditions of Immune Dysregulation – Juvenile Dermatomyositis (JDM)

JDM is traditionally viewed as an autoimmune (adaptive immune) disease. Characteristic clinical signs and symptoms include fatigue, fever, symmetrical weakness of the proximal musculature, and characteristic cutaneous changes consisting of heliotrope discoloration of the

eyelids, which may be accompanied by periorbital edema and erythematous papules over the extensor surfaces of joints (Gottron papules). JDM may also be associated with panniculitis-induced lipodystrophy and metabolic abnormalities, such as hyperlipidemia. Support for a diagnosis of JDM is provided by elevated serum levels of muscle enzymes and the histopathological observation of inflammatory myositis on muscle biopsy. Peripheral blood cells show a characteristic pattern of high expression of IFN regulated genes (known as an IFN signature).

JDM is the most common form of idiopathic inflammatory myopathy in children, with an average age of onset of 7 years. The incidence of JDM in the United States is between 2.5 and 4.1 per million children (Batthish and Feldman 2011). Approximately one third of JDM patients have monocyclic disease that undergoes permanent remission after treatment with standard therapeutic regimens, including corticosteroids. The remaining JDM population has polycyclic disease, a subset of which has more severe disease that is difficult to treat with associated poorer outcomes. In this latter difficult-to-treat population, corticosteroids are used in combination with other immunosuppressive therapies, including, but not limited to, cyclosporine, cyclophosphamide, and intravenous immunoglobulins. Biologic agents, such as intravenous immunoglobulins, anti-TNF agents, and rituximab, are being used in the clinic as a treatment for the more severe subset of JDM patients (Martin et al. 2012). However, patients with severe JDM are frequently unresponsive to therapy and are unable to reduce steroid use without loss of disease control.

It is hypothesized that the pathogenesis of JDM could be explained, at least in part, by an innate immune dysregulation, suggesting that, similar to CANDLE, JDM may be, at least in part, an autoinflammatory disorder as well as an autoimmune disease as these patients exhibit activation of both innate and adaptive immunity. Patients with severe JDM and patients with CANDLE syndrome show similarity of clinical phenotype with myositis and panniculitis being a typical feature of both conditions.

Myositis-associated and -specific autoantibodies have been seen in approximately 40% of JDM patients (Khanna and Reed 2010) and vascular injury with endothelial dysfunction, complement activation, and antibody deposition on small vessels is also apparent and associated with disease progression. Consistent with the contribution of both innate and adaptive immunity to the disease process, increases in circulating IL-6 and type 1 IFN-induced chemokines, including IFN inducible protein 10/ C-X-C motif chemokine 10 (IP-10/CXCL10) and monocyte chemoattractant protein-1, have been reported in JDM patients (Bilgic et al. 2009; Greenberg 2010). Furthermore, these circulating biomarkers are correlated with global visual analog scale (VAS) scores (Bilgic et al. 2009). IL-6 and Type 1 IFNs signal through the JAK-STAT pathway, supporting a hypothesis that inhibition of this pathway could provide a viable therapeutic option.

Summary

Patients with CANDLE, CANDLE-related conditions, SAVI, and severe JDM who are not responsive to at least 1 biologic therapy (except as noted in the inclusion/exclusion criteria), and

who require treatment with oral corticosteroids (≥0.15 mg/kg/day of prednisone or its equivalent) to control systemic signs and symptoms of their syndrome (or, in the opinion of the investigator, have failed an adequate course of steroids or are not suitable candidates for steroid treatment, such as patients with a confirmed genetic diagnosis of CANDLE or SAVI), will be candidates for baricitinib treatment. 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 CANDLE, CANDLE-related conditions, SAVI, and severe JDM for whom biologics have proven to be ineffective, thereby offering these patients an alternative compassionate use therapeutic option.

In Study I4V-MC-JAGA (JAGA), a within-patient dose-escalation treatment regimen of baricitinib will be utilized. Patients will receive an initial dose based upon weight class and eGFR. Patients may then have their dose escalated to determine a tolerable level. Short-term assessment of the potential beneficial effects of baricitinib treatment will be based on a reduction in the average daily diary score and dose of systemic steroids (if the patient is receiving steroids). If treatment with baricitinib appears to be effective, continued treatment with baricitinib may be provided under the provisions of this protocol.

The study will be conducted in compliance with the protocol, good clinical practice (GCP), and applicable regulatory requirements.

5.1. Concept of Autoinflammation

5.1.1. The Role of IL-1 in Autoinflammatory Diseases

The clinical and basic research unraveling of the CIAS1/NLRP3 inflammasome, a crucial platform to activate IL-1β and controlling its release, has revealed a key inflammatory pathway that is not only constitutively activated in CAPS, but also is 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 2011), and cholesterol crystals in coronary artery disease (Goldbach-Mansky 2009; Duewell 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).

5.2. CANDLE Syndrome and Related Non-IL-1 Dependent Autoinflammatory Diseases

An autoinflammatory disorder has recently been characterized that does not respond to treatment with IL-1, TNF, and only partially to IL-6-blocking agents (Liu et al. 2012). CANDLE syndrome 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. 2010; Torrelo et al. 2010).

In an international collaborative effort, 9 patients with the clinical diagnosis of CANDLE syndrome were studied (Liu et al. 2012). Genetic analyses showed that 7 out of 9 patients harbor genetic mutation in PSMB8 of the immunoproteasome complex (i-proteasome). After the original report of CANDLE syndrome 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 **j**oint contractures, **m**uscle atrophy, and **p**anniculitis (Garg et al. 2010). Patients with JMP were recently demonstrated to carry a mutation PSMB8 (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 JMP had more prominent joint contractures and muscle atrophy than patients described as 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 syndrome (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).

5.3. Functional Data Supporting a Rationale to Block IFN Signaling

As mentioned above, empiric treatment with targeted agents to TNF, IL-1, and IL-6 have been unsuccessful. To characterize the inflammatory pathway and to identify therapeutic targets, the cytokine profile, transcriptome, and signaling pathways in these patients has been assessed. Interestingly, IP-10/CXCL10 serum levels, were on average over 77-fold higher than controls. The 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 NOMID, an IL-1 mediated autoinflammatory syndrome, monocytes from CANDLE patients showed stronger STAT-1 phosphorylation in response to all IFN-γ concentrations from 0.1 to 100 IU used for stimulation.

To probe further for 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 ($p<.05$), 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 IPA, 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 the patients received on the IFN-induced genes, blood samples from multiple visits were obtained in 2 patients, including 1 patient treated at different times with anti-TNF-alpha and anti-IL-6 therapy. Although temporary clinical improvement was seen with anti-TNF-alpha and anti-IL-6 treatment (Liu et al. 2012), the "IFN signature" did not improve. IL-6 blocking therapy normalized IL-6 inducible genes and C-reactive protein 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 and STAT-5 were 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.

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

26S proteasomes are multi-subunit protein complexes critical for degradation of polyubiquitynated proteins within cells. The 20S core complex consists of 2 alpha rings and 2 beta rings, each having 7 different alpha (α) or beta (β) subunits. 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 et al. 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 polyubiquitynated 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 syndrome died of cardiac failure at the age of 47. Histological examination of skeletal muscle on autopsy revealed intramitochondrial paracrystalline inclusions and cytoplasmic and myeloid bodies in muscle cells (Oyanagi et al. 1987). Whether the inclusions seen constitute 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.

5.5. In Vitro Evidence for Using a JAK Inhibitor

JAK kinases are critical signaling molecules mediating IFN signaling on the IFN receptors. To determine the effect of a JAK kinase 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).

6. Objectives

6.1. Primary Objective

The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, or JDM results in reduction in the patient's mean daily diary scores as follows:

- CANDLE diary: reduction in mean daily score to <0.5
- SAVI diary: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and respiratory/breathing symptoms score a <1.0 increase from baseline
- JDM diary: reduction in mean daily score exclusive of fever and headache symptoms by ≥0.25.

6.2. Secondary Objectives

The secondary objectives are:

- to determine, in patients receiving steroids at baseline, if administration of baricitinib to patients with CANDLE, CANDLE-related conditions, or SAVI results 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, in patients receiving steroids at baseline, if the administration of baricitinib to patients with severe JDM results in a decrease in the daily dose of corticosteroids (systemic corticosteroids <0.2 mg/kg/day oral prednisone or a decrease of at least 25% of the patient's daily dose at baseline).
- to determine if the administration of baricitinib to patients with severe JDM results in a reduction in the patient's mean diary score exclusive of fever and headache symptoms to <1.0.

7. Investigational Plan

7.1. Summary of Study Design

JAGA is an open-label compassionate use treatment program for patients who weigh at least 8.5 kg and are at least 17.5 months of age (patients who weigh less than 8.5 kg or are younger than 17.5 months may be considered for enrollment after discussion with the Sponsor). Patients will receive an initial dose based on weight class and eGFR. Then the dose may be escalated to determine a tolerable level. 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 steroids), as appropriate.

Screening, Initial Treatment, and Dose Escalation: Screening is a 2- to 28-day period beginning at Visit 1. After receiving written informed consent from the patient or the patient's parent or a legal guardian (hereafter, "parent" refers to "parent or legal guardian") and written assent from the patient (assent is obtained when appropriate—see Section 13.1, Obtaining Informed Consent), patients will be assigned a patient number and will be considered entered into the study and study procedures may begin. Entry procedures will be performed per the Study Schedule (Attachment 1). Patients must complete at least 2 consecutive weeks of diary entries prior to enrollment and receiving the first dose of baricitinib (refer to the Patient Diary and Diary Score section below). If 2 consecutive weeks of diaries, obtained as part of routine care during the 6 weeks prior to entry, are not available at Visit 1, patients can complete the 2 consecutive weeks of diary entries after study consent is signed (study entry) during the screening period, prior to enrollment. Any physical complaints/symptoms that present prior to initiation of treatment with baricitinib will be collected as preexisting conditions on the electronic case report form (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 a serious adverse event (SAE). Information regarding use of concomitant medications will also be collected on the eCRF.

Baricitinib will be dosed by patient weight range and eGFR. See Table JAGA.7.1 for the dosing schedule for patients with eGFR ≥120 mL/min/1.73 m^2 or Table JAGA.7.2 for patients with eGFR <120 mL/min/1.73 m^2. All patients will receive an initial divided (BID or TID)-daily dose. Patients may have their dose escalated, but must receive a dose for at least 72 hours before a dose escalation can occur. Exceeding the maximum doses shown on the dosing tables is an option, but only with consensus in writing between the investigator and the Sponsor that the dose increase is in the best interest of the patient. Safety laboratory data will be assessed according to the Study Schedule (Attachment 1).

Every effort should be made to follow the dose escalation schedule shown in Table JAGA.7.1. However, if a patient's condition warrants an accelerated dose escalation schedule, this may be allowed after consultation with the Sponsor. 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. Where possible, these decisions should be taken following documented agreement between the investigator and Sponsor; however, in emergency situations the investigator may take these actions. In such situations, the Sponsor should be informed as soon as possible. Any subsequent dose restarts or increments will occur only after review of clinical data and documented agreement between the investigator and Sponsor.

Pharmacokinetic Sampling: Blood samples will be collected to determine baricitinib concentrations. Samples will be collected when the patient reaches steady state at the target dose level after approximately 72 hours of treatment. Alternatively, samples may be collected at the next patient visit. Additional details on PK sampling are provided in Section 10.3.2.

Continuing Treatment: Safety laboratory assessments will be performed and reviewed by the investigator along with a copy of the patient's diary at visits according to the Study Schedule (Attachment 1). AEs and concomitant medications will be assessed. Dosing will follow the regimen shown in Table JAGA.7.1 for patients with eGFR ≥120 mL/min/1.73 m^2, and Table JAGA.7.2 for patients with eGFR <120 mL/min/1.73 m^2. Once the patient has reached a stable dose of baricitinib, the same total dose may be administered as equal or unequal divided doses. For patients with eGFR >120 mL/min/1.73 m^2 and weight <20 kg, the total daily dose can be administered up to 4 doses in a day (24 hours). If more than 4 doses are needed in 1 day (24 hours), then consultation and agreement with the Sponsor will be required.

1. If the patient is responding adequately to treatment (average diary score <0.5 or <1.0 [CANDLE or SAVI diaries, respectively] or reduction in average diary score ≥0.25 exclusive of fever and headache symptoms [JDM diary]), the patient will continue receiving baricitinib therapy with follow-up appointments according to the Study Schedule (Attachment 1). Steroid weaning may begin for patients who are receiving steroids. If the patient is responding to treatment, but has not met the threshold to begin steroid weaning and is experiencing new or worsening clinically significant adverse effects from steroids (including, but not limited to, cataracts, vertebral fractures due to osteoporosis, Cushinhgoid 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.

2. If a patient continues to have an inadequate response to the baricitinib dose as evidenced by an elevated diary score (average diary score >0.5 or >1.0 [CANDLE or SAVI diaries respectively] or reduction in average diary score <0.25 exclusive of fever and headache symptoms [JDM diary]) or ongoing clinical disease activity reflected by increased symptoms or elevated markers of inflammation, the dose should be increased in the dose escalation steps shown in Table JAGA.7.1 or Table JAGA.7.2. The reason for dose increase will be documented in the medical record. Patients must have received a dose for at least 72 hours before continuing to the next dose increase. Every effort should be made to follow the dose escalation schedule shown in Table JAGA.7.1. However, if a patient's condition warrants an accelerated dose escalation schedule, this may be allowed after consultation with the Sponsor.
3. If a patient reaches the maximum allowable dose as specified in (Table JAGA.7.1 or Table JAGA.7.2) and has an inadequate response to treatment, the patient may be discontinued from the study to pursue other treatment options, or one or both of the following may be considered after consultation with the Sponsor:
    (1) Once the patient has reached a stable dose of baricitinib, the same total daily dose may be administered at greater frequency as equal or unequal divided doses (up to 4 doses in 1 day [24 hours]).
    (2) The patient's dose may be increased above the maximum dose shown in Table JAGA.7.1 or Table JAGA.7.2 if, in the opinion of the investigator, this dose increase is warranted based on the clinical assessment of the patient, evaluation of available PK data, and evaluation of renal function. The Sponsor must be consulted before the dose is increased in excess of the maximum dose shown in the dosing tables. For each affected study patient, the conclusion of this consultation must be documented in a way that confirms consensus between the investigator and the Sponsor.
4. If a patient continues to have an inadequate response to treatment after considering the dose modification options identified in item 3 above, then the patient will be discontinued from baricitinib. The patient will return for a follow-up safety visit approximately 28 days after their last dose of investigational product and will discontinue from the study.
5. If a patient reaches the maximum allowable dose (or had a dose modification as described in item 3 above) and his or her average diary score has decreased, but has not met the threshold for adequate response/steroid weaning (does not reach an average diary score of <0.5 or <1.0 [CANDLE or SAVI diaries, respectively] or does not achieve a reduction in the average diary score by ≥0.25 exclusive of fever and headache symptoms [JDM diary]), the patient may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment.

Follow-up appointments will continue during the treatment period according to the Study Schedule (Attachment 1). Each patient's concomitant medications, investigational product compliance, height, weight, vital signs, and AEs will be assessed; and routine chemistry,

hematology, and urinalysis assessments will be performed according to the Study Schedule (Attachment 1). A physical exam will be conducted according to the Study Schedule (Attachment 1).

As the conditions being treated in this compassionate use program are rare, patients may be enrolled who must travel a considerable distance to the investigative site. For most of the required visits patients should be seen in-person at the investigative site. Once patients achieve a stable dose, some required visits may be performed as a telephone visit. If a telephone visit is performed, laboratory samples should be obtained locally. Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. An optional 4-week washout period (Visit 801) is included to allow monitoring of patient safety after discontinuing baricitinib treatment in JAGA.

Baricitinib will be provided to an individual patient for up to 288 weeks. As additional safety information is obtained from ongoing clinical trials for baricitinib, additional access to baricitinib for a longer period of time will be considered. After the trial period under this study, the Sponsor will assess the benefit/risk balance for continued access to baricitinib. If no new safety concerns are detected, this study may be amended to allow for continued dosing of baricitinib for another set period of time. Figure JAGA.7.1 illustrates the study design.

Table JAGA.7.1. Dose Escalation Schedule for Patients with eGFR ≥120 mL/min/1.73 m^2

Initial Dose

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	≥120	2 mg	2 mg	2 mg	6 mg	72 hours	0.3/NA	TID
20-40 kg	≥120	3 mg	—	3 mg	6 mg	72 hours	0.15/0.3	BID
>40 kg	≥120	4 mg	—	4 mg	8 mg	72 hours	NA/0.2	BID

First Dose Escalation

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	≥120	2 mg	2 mg 2 mg	2 mg	8 mg	72 hours	0.4/ NA	QID
20-40 kg	≥120	3 mg	2 mg	3 mg	8 mg	72 hours	0.2/0.4	TID
>40 kg	≥120	5 mg	—	5 mg	10 mg	72 hours	NA/ 0.25	BID

Second Dose Escalation (only in patients > 40 kg)

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
>40 kg	≥120	6 mg	—	6 mg	12 mg	72 hours	NA/0.3	BID

Abbreviations: max = maximum; min = minimum; NA = not applicable.

— indicates no further dose escalation allowed.

a See Section 9.4 if a change in the patient's weight during the study would place the patient in a different weight range.

b After reaching a stable dose, the total daily dose can be administered as equal or unequal divided doses.

c Duration of treatment prior to escalation includes days to obtain samples and results from safety blood test assessments prior to the first dose or first dose increase.

d Dose in mg/kg for the lowest weight and highest weight in each weight class.

Table JAGA.7.2. Dose Escalation Schedule for Patients with eGFR <120 mL/min/1.73 m^2

Initial Dose[a]

Weight Class[b]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	<120	2 mg	—	2 mg	4 mg	72 hours	0.2/NA	BID
20-40 kg	<120	2 mg	—	2mg	4 mg	72 hours	0.1/0.2	BID
>40 kg	<120	2 mg	—	2 mg	4 mg	72 hours	NA/0.1	BID

First Dose Escalation (only for patients with eGFR ≥ 60 mL/min/1.73 m^2)

Weight Class[b]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	60-119	2 mg	2 mg	2 mg	6 mg	72 hours	0.3/NA	TID
20-40 kg	60-119	3 mg	—	3 mg	6 mg	72 hours	0.15/0.3	BID
>40 kg	60-119	3 mg	—	3 mg	6 mg	72 hours	NA/0.15	BID

a Baricitinib should not be used in patients with eGFR < 30 mL/min/1.73 m^2.

b See Section 9.4 if a change in the patient's weight during the study would place the patient in a different weight range.

c Duration of treatment prior to escalation includes days to obtain samples and results from safety blood test assessments prior to the first dose or first dose increase.

d Dose in mg/kg for the lowest weight and highest weight in each weight class.

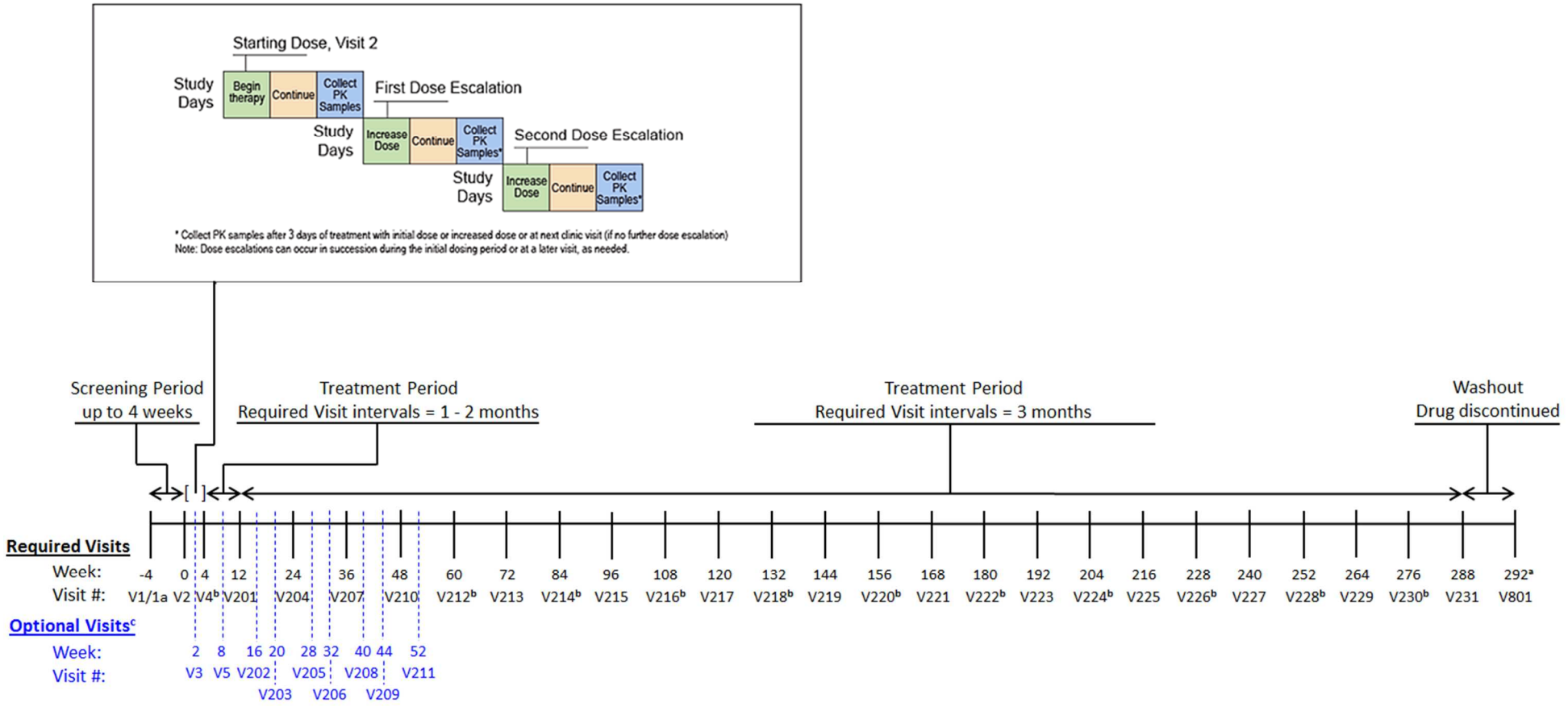

Figure JAGA.7.1. Protocol I4V-MC-JAGA study design.

Abbreviations: PK = pharmacokinetics; V = visit.

a V801 (optional) should occur approximately 28 days after the last dose of investigational product.

b These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, laboratory samples should be obtained and tested locally, and a copy of the laboratory report sent to the PI.

c Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained and tested locally, and a copy of the laboratory report sent to the PI.

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 (that is, CANDLE, JDM, or SAVI). The patient diaries are shown in Attachment 4. 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. During clinic visits, it is preferable that the patient or caregiver complete the patient diary rather than site staff.

The patient or caregiver will be instructed to rate each symptom (fever, rash, musculoskeletal pain, and fatigue [all diaries], headache [CANDLE and JDM diaries], weakness [JDM 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]). 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.

The diary is to be completed daily throughout the study. The diary score is used to assess disease activity and inform the need for an additional dose increase (up to the maximum allowed dose as detailed in Table JAGA.7.1) or initiation of steroid weaning as described (if the patient is receiving steroids). At each visit, the investigator will calculate the average score for each symptom being collected on the diary (that is, the average of the daily scores since the previous visit, correcting for any day for which diary scores were not recorded). The investigator 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. An average diary score ≥ 0.5 (CANDLE diary) or ≥ 1.0 (SAVI diary) or a reduction in the average diary score of <0.25 exclusive of fever and headache symptoms (JDM diary), or ongoing clinical disease activity reflected by increased symptoms not captured on the diary will be indicative of a lack of complete response and will trigger a dose escalation. An average diary score <0.5 (CANDLE diary) or <1.0 (SAVI diary) or a reduction in the average diary score ≥ 0.25 exclusive of fever and headache symptoms (JDM diary) will be indicative of a response to treatment and may trigger initiation of steroid weaning (if the patient is receiving steroids). Additionally, if the patient is responding to treatment, but has not met the average diary score threshold to begin steroid weaning and is experiencing new or worsening clinically significant adverse effects from steroids (including, but not limited to, cataracts, vertebral fractures due to osteoporosis, Cushinhgoid 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. The investigator should review the entire diary and

average diary scores at each visit. If there is a trend in the diary scores, (that is, 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.

Patients whose average diary scores decrease after receiving the maximum allowable dose level of baricitinib (as defined in Table JAGA.7.1 or Table JAGA.7.2), but do not meet the threshold for steroid weaning (for patients receiving steroids at baseline), or an adequate response (do not reach an average daily CANDLE diary score <0.5 or SAVI diary score <1.0, or do not achieve a reduction in the JDM diary score of ≥0.25 exclusive of fever and headache symptoms), may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment. This will not be considered to be a protocol violation.

7.2. Discussion of Design and Control

This compassionate use study is an open-label, single-arm design intended to provide baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, or severe JDM. Baricitinib has not been investigated in children; therefore, patients will receive an initial dose that may be escalated using dose escalation tables to an effective and tolerable dose. The dose-escalation period allows for safety assessments in between dose escalations. This study, by the nature of compassionate use, is not intended to answer any research hypothesis; however, it is intended to provide a potential treatment for inflammatory conditions proven resistant to other therapies. Though the open-label, single-arm design has potential for the introduction of bias, the study design represents an ethical approach for treatment of these conditions within a compassionate use framework. An optional 4-week washout period (Visit 801) is included to allow monitoring of patient safety after discontinuing baricitinib treatment in JAGA.

Continued ongoing inflammation at the organ level causes organ damage and results in significant morbidity and mortality. 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 and unsustainable chronic doses of steroids, a compassionate use study is appropriate.

8. Study Population

Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder such as CANDLE syndrome, CANDLE-related syndrome, or SAVI or will have been diagnosed with severe JDM.

Patients who meet all of the inclusion criteria (Section 8.1) and do not meet any of the exclusion criteria (Section 8.2) may enter the study (that is, sign consent). In addition, patients must meet the enrollment criteria (Section 8.3) in order to be eligible to receive baricitinib. Given the severity of these diseases and the absence of other therapeutic options, any patient that does not meet inclusion, exclusion, and/or enrollment criteria may still be considered for enrollment upon consultation with the Sponsor and assessment of the benefits and risks.

8.1. Inclusion Criteria

Patients are eligible for entry into the study (that is, eligible to sign consent) only if they meet **all** of the following criteria:

1) Have systemic signs and symptoms of inflammation as manifested by the presence of 2 or more of the following symptoms: rash, fever, musculoskeletal pain, headache, fatigue, weakness, respiratory/breathing symptoms, or ulcers/ischemic lesions.

2) Have an average daily diary score of ≥0.5 (CANDLE diary) or ≥1.0 (SAVI diary) or ≥1.0 exclusive of headache and fever symptoms (JDM diary) assessed over at least 2 consecutive weeks during the 6 weeks prior to entry, if available. Otherwise, patients can complete the diary after study consent is signed during the screening period and meet the inclusion criteria for enrollment into the study.

3) Are ≥17.5 months of age. Patients younger than 17.5 months of age can be considered for enrollment after discussion with the Sponsor.

4) Are ≥8.5 kg in body weight. Patients weighing less than 8.5 kg can be considered for enrollment after discussion with the Sponsor.

5) Have been previously treated with at least 1 biologic therapy and, in the opinion of the investigator, did not respond or are no longer responding to therapy. If the patient has been diagnosed with CANDLE or an equivalent syndrome with decreased proteasome function, or SAVI, the need for previous biologic therapy is not required.

6) Require treatment with oral corticosteroids (≥0.15 mg/kg/d of prednisone or its equivalent) for control of systemic signs and symptoms of their chronic inflammatory disease for at least 2 weeks prior to study entry, or in the opinion of the investigator, have failed an adequate course of steroids. Exceptions to this criterion are patients with a confirmed genetic diagnosis of SAVI or CANDLE.

7) Have had previous documented elevations in acute-phase reactants (for example, high sensitivity C-reactive protein) considered to be the result of the inflammatory disease (patients with CANDLE or CANDLE-related conditions only).

8) Have the ability to provide informed consent or have a legal representative who is willing and able to provide written informed consent, provided that assent is obtained from patients at an age-appropriate level.

8.1.1. Patients with Juvenile Dermatomyositis

Patients with JDM are eligible for entry into the study (that is, eligible to sign consent) only if they meet **all** of the previous criteria (1 through 8) and all of the following criteria:

37) Meet definite or probable JDM diagnosis by the criteria of Bohan and Peter (1975) (Attachment 6) with onset of first symptom prior to 18 years of age.

38) Have refractory myositis as defined by the intolerance to, or an inadequate response to, corticosteroids plus an adequate regimen of at least 2 other immunomodulatory or immunosuppressive agents (including at least 1 biologic agent), such as intravenous immune globulin (IVIg), azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, tacrolimus, or cyclosporine A. Other immunomodulatory or immunosuppressive agents, such as rituximab, can be considered after discussion with the Sponsor. The definition of intolerance is side effects that require discontinuation of the medication or an underlying condition that precludes the further use of the medication.

- Adequate treatment with corticosteroids or immunosuppressive/ immunomodulatory drugs is defined as the lowest of the following doses:
    - Corticosteroids: 1.0 mg/kg/d or 60 mg/d for at least 1 month
    - Azathioprine: 2 mg/kg/d or 150 mg/d for at least 3 months
    - Methotrexate: 0.3 mg/kg or 15 mg/m^2/week or 15 mg/week for at least 3 months
    - IVIg: 1 g/kg/month or 60 g/month for at least 3 months
    - Mycophenolate mofetil: 30 mg/kg/d or 1000 mg twice daily for at least 3 months
    - Cyclophosphamide: 1.0 mg/kg/d or 500 mg/m^2/month or 500 mg/month intravenously for at least 3 months
    - Tacrolimus: 0.1 mg/kg/d or 5 mg/d for at least 3 months
    - Cyclosporine: 2.5 mg/kg/d for at least 3 months

39) If receiving hydroxychloroquine, must have been receiving a stable dose for at least 4 weeks prior to screening visit

40) If receiving a statin, must have been receiving a stable dose for at least 8 weeks prior to screening visit.

8.1.2. Patients with CANDLE-Related Conditions

Patients with CANDLE-related conditions are eligible for entry into the study (that is, eligible to sign consent) only if they meet all of the common inclusion criteria (1 through 8) and all of the following criteria:

46) Have organ specific inflammation involving at least one of the following: vasculopathy (such as arterial hypertension, pulmonary hypertension, vascular calcifications such as basal ganglia calcifications, or livedo reticularis), metabolic changes (such as lipodystrophy, dyslipidemia, insulin resistance, or intra-abdominal fat deposition), musculoskeletal manifestations (myositis, arthralgias or arthritis, and/or panniculitis), hematological manifestations (i.e. cytopenias) and/or interstitial lung disease.

47) Have a history of high IP-10/CXCL10 levels and/or IFN response signature in peripheral blood mononuclear cells being one of the most dysregulated blood signatures.

8.2. Exclusion Criteria

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

9) Have received an immunosuppressive biologic agent/monoclonal antibody within 4 half-lives prior to entry, for example, anakinra (4 half-lives=18 hours); etanercept (4 half-lives=18 days); infliximab; or adalimumab (4 half-lives=36 days). Use of IVIg is permitted. Exceptions may be considered after discussion with the Sponsor.

10) Are pregnant or nursing at the time of entry

11) Are females of childbearing potential who do not agree to use 2 forms of highly effective 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 investigational product

    Females of nonchildbearing potential are defined as women ≥60 years of age, women ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, or women who are congenitally or surgically sterile (that is, have had a hysterectomy or bilateral oophorectomy or tubal ligation).

    The following birth control methods are considered highly effective (the patient should choose 2 to be used with their male partner):

    - oral, injectable, or implanted hormonal contraceptives
    - condom with a spermicidal foam, gel, film, cream, or suppository
    - occlusive cap (diaphragm or cervical/vault caps) with a spermicidal foam, gel, film, cream, or suppository

- intrauterine device
- intrauterine system (for example, progestin-releasing coil)
- vasectomized male (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate)

  Note: when local guidelines concerning highly effective methods of birth control differ from the above, the local guidelines must be followed.

12) Are males who do not agree to use 2 forms of highly effective birth control (see above) 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 investigational product.

13) Have had symptomatic herpes zoster infection within 12 weeks prior to entry or during the screening period

14) Have a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster, central nervous system involvement, postherpetic neuralgia)

15) Have evidence of active infection, at the time of entry or during the screening period, that, in the opinion of the investigator, would pose an unacceptable risk for participating in the study.

16) Have a history of active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).

17) Have documented high titer autoantibodies suggestive clinically of autoimmune diseases other than severe JDM.

18) Are immunocompromised and, in the opinion of the investigator, are at an unacceptable risk for participating in the study.

19) Have had a serious systemic or local infection (including an infectious mononucleosis-like illness or herpes zoster) within 12 weeks prior to entry or during the screening period. Exceptions include SAVI patients with infected ulcerative skin lesions, which in the opinion of the investigator, would not pose an unacceptable risk for pariticipating in the study.

20) Have been exposed to a live vaccine within 12 weeks prior to entry or are expected to need/receive a live vaccine (including herpes zoster vaccination) during the course of the study

    Note: Investigators should review the vaccination status of their patients and follow the local guidelines for vaccination with nonlive vaccines intended to prevent infectious disease prior to entering patients into the study.

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

22) 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.

23) Have an estimated glomerular filtration rate (eGFR) based on the most recent available serum creatinine of <40 mL/min/1.73 m^2.

24) Have or have had a history of lymphoproliferative disease; or 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.

25) Have a history of chronic alcohol abuse or intravenous drug abuse within the 2 years prior to entry.

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

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

28) Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or non-approved use of a drug or device (other than the investigational product used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

8.2.1. Patients with Juvenile Dermatomyositis

Patients with JDM will be excluded from the study if they meet **any** of the previous criteria (9 through 28) or any of the following criteria:

41) Have drug-induced myositis (myositis in patients taking medications known to induce myositis-like syndromes, including, but not limited to, statin agents, fibric acid derivatives, colchicine, and hydroxychloroquine).

42) Have a history of juvenile polymyositis, inclusion body myositis, or cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer except basal or squamous cell skin cancer or carcinoma in situ of the cervix if at least 5 years since excision.

43) Have myositis in overlap with another connective tissue disease (CTD) that precludes the accurate assessment of a treatment response (for example, difficulty in assessing muscle strength in a scleroderma patient with associated myositis).

44) Have joint disease or other musculoskeletal condition, which precludes the ability to quantitate muscle strength.

8.3. Enrollment Criteria

8.3.1. Inclusion Criteria for Study Enrollment

Entered patients are eligible for enrollment into the study (that is, eligible to receive baricitinib) only if they continue to meet **all** of the common inclusion criteria and applicable disease-specific inclusion criteria for entry (Section 8.1) at the time of Visit 2 plus the following requirement(s):

29) Have a mean daily diary score of ≥0.5 (CANDLE diary) or ≥1.0 (SAVI diary) or ≥1.0 exclusive of headache and fever symptoms (JDM diary) assessed over at least 2 consecutive weeks during the 6 weeks prior to entry or after entry but prior to enrollment for patients who completed the diary after consent was signed.

45) For JDM patients, have severe disease as assessed by core set measures (Attachment 6). Severe disease will be assessed as follows: three of the following six abnormal core set measures:

- Baseline manual muscle testing (within the previous month) with a score no greater than 125 out of a possible 150
- Parent/patient global VAS with a minimum value of 2.0 cm on a 10 cm scale (Attachment 7).
- Physician global VAS with a minimum value of 2.0 cm on a 10-cm scale (Attachment 8).
- Childhood Health Assessment Questionnaire or Health Assessment Questionnaire disability index of ≥0.25.
- Elevation of at least one of the muscle enzymes (creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase [ALT], and aspartate aminotransferase [AST]) at a minimum level of 1.3 × the upper limit of normal (ULN).
- Global extramuscular disease activity score with a minimum value of 1.0 cm on a 10-cm VAS scale (this measure is the physician's composite evaluation and is based on assessments of activity scores on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac scales of the Myositis Disease Activity Assessment Tool (Attachment 9).

8.3.2. Exclusion from Study Enrollment

Entered patients are ineligible for enrollment (that is, ineligible to receive baricitinib) and should be discontinued from the study if they meet any of the following criteria:

30) Have screening laboratory test values outside the reference range for the population or investigative site that, in the opinion of the investigator, pose an unacceptable risk for the patient's participation in the study.

31) Have any of the following specific abnormalities on screening laboratory tests:

- AST or ALT >2 × ULN unless the hepatitis is confirmed as resulting from the autoinflammatory condition. If autoinflammatory-associated hepatitis is present, AST or ALT cannot exceed 4 × ULN. If inflammatory myositis is present or suspected, obtain total and direct bilirubin, aldolase, and gamma-glutamyl transferase if not yet done. Elevation in AST and/or ALT is acceptable if gamma-glutamyl transferase and total and direct bilirubin are less than 1.5 × ULN and an expert independent of the principal investigator (preferably a hepatologist or gastroenterologist) documents that the elevation is secondary to myositis. Even if inflammatory myositis is considered present, AST or ALT cannot exceed 5 × ULN.
- Hemoglobin <10 g/dL (100 g/L). Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with hemoglobin <10 g/dL if the anemia is considered a result of the underlying disease (see below).
- Total WBC count <2500 cells/μL. Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with WBC count <2500 cells/μL if the low WBC count is considered a result of the underlying disease (see below).
- Neutropenia (absolute neutrophil count [ANC] <1200 cells/μL). Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with an ANC <1200 cells/μL if the low ANC is considered a result of the underlying disease (see below).
- Thrombocytopenia (platelets <100,000/μL). Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with a platelet count <100,000/μL if the low platelet count is considered a result of the underlying disease (see below).
- eGFR <40 mL/min/1.73 m^2

Note: A patient with CANDLE, CANDLE-related condition, or SAVI may be enrolled with any of the above specific abnormalities on screening laboratory tests if these laboratory abnormalities are considered a feature of the disease. An expert independent of the principal investigator (preferably a hematologist) must evaluate the patient and, in conjunction with the principal investigator, document that the laboratory abnormality is a feature of the underlying CANDLE, CANDLE-related condition, or SAVI condition; the investigator must also consult with the Sponsor before the patient can be enrolled.

32) Have screening thyroid-stimulating hormone and/or thyroxine values outside of the laboratory's reference range and are assessed to be clinically significant. If results are available from testing within 1 month, 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, laboratory tests may be repeated once within 1 week of the initial values, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

33) 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 (for example, Bazett's corrected QT interval >450 msec for males and >470 msec for females).

34) Have evidence of active or latent TB as documented by a positive purified protein derivative (PPD) test (≥5 mm induration between approximately 2 and 3 days after application, regardless of vaccination history), medical history, and chest x-ray at screening. If results are available from testing within 1 month, then the patient will not have to be retested. Exceptions include patients with a history of latent TB who have documented evidence of completing a course of appropriate treatment:

- If the PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active or latent TB, the patient should have a QuantiFERON®-TB Gold test. If the test is positive or indeterminate, the patient is excluded from the study.
- The QuantiFERON®-TB Gold test may be used instead of the PPD test; patients with positive tests are excluded. If the QuantiFERON-TB Gold test is indeterminate, a retest is allowed. If the retest is also indeterminate, the patient is excluded from the study.

35) Have a positive test for hepatitis B defined as (1) positive for hepatitis B surface antigen, or (2) positive for anti-hepatitis B core antibody, but negative for hepatitis B surface antibody unless the anti-hepatitis B core antibody is thought to be a false positive result. In the latter case, confirmation of the presence of hepatitis B virus (HBV) by DNA testing is required. An HBV DNA indeterminate result is considered HBV infection.

    If results are available from testing within the previous 3 months, then the patient will not have to be retested:

- If any of the hepatitis B tests have an indeterminate result, confirmatory testing will be performed by an alternate method.

36) Have hepatitis C virus (positive for anti-hepatitis C antibody with confirmed presence of hepatitis C virus); have evidence of HIV infection, and/or positive HIV antibodies. If results are available from testing within the previous 3 months, then the patient will not have to be retested.

Patients who are entered, but do not meet enrollment criteria, should be discontinued from the study. These patients can be re-entered into the trial (that is, be reconsented) if the investigator believes that the patient might meet enrollment criteria at a future date, taking into consideration the volume of blood required for rescreening.

8.4. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [9] excludes individuals taking medications that may confound or may interfere with the ability to assess the safety and efficacy of baricitinib. Exclusion Criteria [10] to [12] exclude individuals who are pregnant, breastfeeding, at risk for becoming pregnant, or at risk for impregnating their partner during the study. Exclusion Criteria [13] to [21] and [34] to [36] exclude individuals who are at an increased risk for infections or infectious complications. Exclusion Criteria [22] to [25] and [30] to [33] exclude individuals with concomitant medical conditions that increase the risk for their participation in the study. Exclusion Criteria [26] to [28] exclude individuals who may not be compliant with study-related procedures or whose participation in the study may introduce bias. Exclusion Criteria [41] through [44] exclude JDM patients who may have another myositis condition that would preclude accurate muscle strength assessment.

8.5. Discontinuations

8.5.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be discontinued from the investigational product, but may be allowed to continue in the study in order to provide follow-up data. An exception may be granted in rare circumstances where the patient has a serious or life-threatening condition for which there is no effective alternative therapy and, in the opinion of the investigator, is receiving benefit from investigational product. In these rare cases, the investigator must obtain documented approval from Eli Lilly and Company (Lilly) to allow the patient to continue to receive investigational product.

8.5.2. Interruption of Investigational Product

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 the Sponsor must be contacted to discuss and document the appropriate course of action which may include a nephrology evaluation.

As listed in Table JAGA.8.1, certain situations necessitate a discussion with the Sponsor 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 JAGA.8.1 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 JAGA.8.1. Guidance on Interruption of Investigational Product

Hold investigational product if the following laboratory test results occur, unless continuation of investigational product is approved by the Sponsor with documentation:	If investigational product was stopped, it may be restarted after discussion with the Sponsor or when:	Additional instructions:
WBC count <2,000 cells/µL[a]	WBC count ≥2,000 cells/µL	None
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.)	None
Lymphocyte count <500 cells/µL[a]	Lymphocyte count ≥500 cells/µL	None
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.)	None
eGFR <40 mL/min/1.73 m^2 (from serum creatinine)[b]	eGFR ≥40 mL/min/1.73 m^2	Repeat BK titers in blood and urine. Nephrology evaluation may be indicated
ALT or AST >5 x ULN or ALT or AST >3 x ULN and total bilirubin >2 x ULN	ALT and AST return to <2 x ULN, and investigational product is not considered to be the cause of enzyme elevation.	See Recommended Hepatic Evaluation Guidance Document (Attachment 3).
Hemoglobin <8 g/dL[a]	Hemoglobin ≥8 g/dL	None
HBV DNA ≥ lower limit of quantification [c]	At the discretion of the investigator after consultation with the Sponsor.	None
Malignancy	At the discretion of the investigator after consultation with the Sponsor.	None
Pregnancy	At the discretion of the investigator after consultation with the Sponsor.	None

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; ULN = upper limit of normal; 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. An expert independent of the principal investigator (preferably a hematologist) must evaluate the patient and, in conjunction with the principal investigator, determine and document that the laboratory abnormality is related to the underlying disease; the investigator must also consult with the Sponsor 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 the Sponsor, 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 pre-existing renal impairment, a lower threshold for interruption may be considered after discussion with the Sponsor.

[c] If a HBV DNA result of 'target detected'(above the lower limit of quantification), then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study drug 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.

8.5.2.1. Discontinuation from Investigational Product

Any patient who is permanently discontinued from investigational product for an abnormal laboratory result should have the abnormal laboratory result reported as an AE, or an SAE if the laboratory abnormality results in an outcome requiring the AE to be reported as an SAE.

In addition, patients may be discontinued from the investigational product or from the study 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.
  - 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.
    - It is possible that a JAK inhibitor similar to Lilly's baricitinib may become commercially available before baricitinib. Once a JAK inhibitor becomes commercially available, Lilly's compassionate use program for baricitinib may be discontinued. Should another medication with potential to treat this patient population become commercially available before Lilly's baricitinib, the compassionate use program for baricitinib may be discontinued.

- 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.
- Adverse Event
  - The investigator decides that the patient should be withdrawn. If this decision is made because of an SAE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations Section 10.2.

Patients who discontinue the investigational product and/or study early will have end-of-study procedures performed as shown in the Study Schedule (Attachment 1).

8.5.3. Discontinuation of Study Sites

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

8.5.4. 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.

9. Treatment

9.1. Treatments Administered

All eligible patients will receive treatment with baricitinib as a twice-daily dose or multiple divided doses (as described in Section 7.1). Depending upon the prescribed dose and/or the visit number, the dosing will occur during the patient's clinic visit, or packaged baricitinib will be dispensed to the patient to provide enough medication for dosing until the next visit.

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the patient, parent, or legal guardian, verifying that instructions are followed properly, maintaining accurate records of investigational product dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

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

9.2. Materials and Supplies

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

During clinic visits, investigational product may be prepared by a pharmacist or other qualified person using good pharmacy practices. Tablets are not to be split for the purpose of dose adjustment without documented approval from the Sponsor for each individual case.

Investigational product will be dispensed to the patient at the investigator's study site. As needed, preparation instructions will be provided by the clinical site. Investigational product packaging will be labeled with a unique identifier for drug accountability. Investigational product will be dispensed with additional tablets to allow for sufficient supply.

9.3. Method of Assignment to Treatment

All patients participating in this study will receive open-label baricitinib.

9.4. Rationale for Selection and Timing of Doses in the Study

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 JAGA.7.1 or Table JAGA.7.2 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 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, initial improvements in clinical status were only observed upon achieving a stable 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 autoinflammatory syndromes appears to require higher concentrations of disease-modifying antirheumatic 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 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.

Subsequently, based on PK analyses of additional patients in the JAGA program, body weight and renal function (GFR estimated by the Schwartz equation for patients under 18 years and by CKD-EPI for patients older than 18 years) were identified as significant covariates on the apparent volume of distribution (V/F) and apparent clearance (CL/F), respectively, which supports dose adjustments based on weight and eGFR. Among JAGA patients with normal renal function, the observed baricitinib elimination half-life was < 6 hours in nearly all patients. The weight categories and dosing regimens presented in Table JAGA.7.1 and Table JAGA.7.2 are based on observed dose titration and stable dose in the 18 JAGA patients seen at NIH up to 04 March 2016 and the PK analyses from these patients.

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 JAGA.7.1 for patients with eGFR ≥ 120 mL/min/1.73 m^2 and Table JAGA.7.2 for patients with eGFR < 120 mL/min/1.73 m^2. If the patient loses weight during the study, the investigator may opt to keep the patient on their current dose. The investigator should ensure that the increase in weight is not related to fluid retention.

9.5. 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 STAT3-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.

9.6. Continued Access to Investigational Product

Patients may receive baricitinib for up to 288 weeks under the terms of this study.

This study may be terminated at the time of United States commercial availability of baricitinib or at the time of United States commercial availability of a similar JAK inhibitor or another drug

with potential to treat these patients. Baricitinib will no longer be supplied if Lilly stops development of baricitinib for any reason at any time.

9.7. Blinding

This is an open-label study.

9.8. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication eCRF.

9.9. Treatment Compliance

Patient compliance with investigational product will be assessed at each visit. Compliance will be assessed by counting returned tablets. 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.

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Primary Effectiveness Measure

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

10.2. Safety Evaluations

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.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that cause patients to discontinue before completing the study. The patients should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

10.2.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to investigational product or drug-delivery system should be reported. Data on fetal outcome and breast feeding are collected for regulatory reporting and drug-safety evaluation.

Study-site personnel will record the occurrence and nature of each patient's preexisting conditions, including autoinflammatory diseases under treatment in the study.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to study procedures are reported to Lilly or designee.

In addition, all AEs occurring after the patient receives the first dose of investigational product must be reported to Lilly or its designee via eCRFs.

Any clinically significant findings from ECGs, laboratory values, vital-sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to study procedure, studied disease state, investigational product, and/or drug-delivery system via the eCRF.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study-site personnel must clearly report to Lilly or its designee via the eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.2.1.1. Serious Adverse Events

SAE collection begins after the patient has signed informed consent and has received investigational product. If a patient experiences an SAE after signing informed consent, but prior to receiving investigational product, the event will NOT be collected unless the investigator feels the event may have been caused by a study procedure.

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

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. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs occurring after a patient has taken the last dose of investigational product will be collected in the pharmacovigilance system and the clinical data-collection database for 28 days after the last dose of investigational product, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either investigational product, or drug delivery system, or a study procedure.

SAEs that could be expected in the study population independent of drug exposure will be assessed by the Sponsor in aggregate periodically during the course of the trial are not currently defined.

10.2.1.1.1. 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 recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance documents.

10.2.1.2. Adverse Events of Special Interest

Adverse events of special interest include the following:

- infections
- myelosuppressive events of anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia
- thrombocytosis
- elevations in ALT/AST (>3 times ULN) with total bilirubin (>2 times ULN)

Patients with these events will be identified using the same criteria presented in Section 8.5.2 for the interruption of investigational product (Table JAGA.8.1) with the exception of anemia, which will be defined as a hemoglobin <6.5 g/dL, and thrombocytosis, which will be defined as a platelet count >600,000/µL.

10.2.2. Other Safety Measures

10.2.2.1. Electrocardiograms

Twelve-lead ECGs will be obtained according to the Study Schedule (Attachment 1). A single 12-lead ECG measurement will be performed at screening. This screening ECG will be interpreted by a qualified physician (the investigator or qualified designee) at the site to determine whether the patient meets entry criteria.

10.2.2.2. 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 pre-existing 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 (Attachment 1).

10.2.2.3. Vital Signs

Vital signs (e.g. blood pressure and pulse) will be measured at times indicated in the Study Schedule (Attachment 1). 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.

10.2.2.4. Chest X-Ray and Tuberculosis Testing

A posterior-anterior view chest x-ray will be obtained, unless results from a chest x-ray obtained within 6 months prior to the study are available and are either normal or show only stable disease. The chest x-ray will be reviewed by the investigator or his/her designee to exclude patients with active TB infection.

In addition, patients will be tested at screening for evidence of active or latent TB indicated by a positive PPD TB skin test response (≥5 mm induration, between approximately 2 and 3 days after test application [visits as indicated on the Study Schedule, Attachment 1], regardless of Bacille Calmette-Guérin vaccination history). If the QuantiFERON-TB Gold test is available and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may be used instead of the PPD TB test (positive tests excluded) and may be read locally. If the QuantiFERON-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

Patients who have a documented history of completing an appropriate TB treatment regimen with no history of re-exposure since their treatment was completed are eligible to participate in the study.

10.2.2.5. Liver-Function Monitoring

Liver-function monitoring will occur frequently throughout the study. If elevations in ALT/AST or total bilirubin occur, the patient should be closely observed as described in Table JAGA.8.1 and the Recommended Hepatic Evaluation Guidance Document (Attachment 3).

10.2.2.6. 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, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide. During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased. See Attachment 1 for frequency of pulmonary function monitoring.

10.2.2.7. 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 Attachment 1.

10.2.3. Safety Monitoring

Lilly will review SAEs within time frames mandated by company procedures. 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 8.5 for discontinuation criteria related to specific AEs.

Vitals signs will be monitored as indicated in the Study Schedule (Attachment 1).

Twelve-lead ECGs will be reviewed for safety. In addition, unscheduled ECGs may be recorded for safety assessments, if clinically indicated.

10.2.4. Complaint Handling

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

Complaints related to unblinded concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.3. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study.

Attachment 1 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study. Fewer invasive sampling may actually occur, but this will not require a protocol amendment.

10.3.1. Samples for Standard Laboratory Testing

Blood and urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, including chemistry, hematology, and urinalysis panels, will be performed. Every effort should be made to obtain all laboratory tests listed in Attachment 2; however, if laboratory tests are not available locally or test results are otherwise missing, this will not be considered a protocol violation. A pregnancy test will be performed (if applicable). Attachment 2 lists the specific tests that will be performed for this study.

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.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.3.2. Samples for Drug Concentration Measurements Pharmacokinetics

Venous blood samples for the measurement of baricitinib concentrations will be collected from all patients enrolled in the study. Samples will be collected after beginning baricitinib therapy and at each dose increase at the time points shown in Table JAGA.10.1. It is also recommended that PK samples be collected more frequently for patients with eGFR < 120 mL/min/1.73 m^2, which may be at every visit if deemed necessary.

Table JAGA.10.1. Pharmacokinetic Sampling

Sampling at Beginning of Treatment and at Each Dose Increase		
Day 1, Start of therapy or day of dose increase	Baricitinib administered at initial dose or baricitinib dose increased (Table JAGA.7.1)	
Day 2	Continue baricitinib	
Day 3 or next clinic visit[a] (if no further dose increase)	Continue baricitinib	Collect 4 PK samples at morning dose: • Pre-morning-dose • 1 hour post-morning-dose • 1.5 hours post-morning-dose • 4 hours post-morning-dose Collect 2 PK samples at evening dose: • Pre-evening-dose • 1.5 hours post-evening-dose

Abbreviations: PK = pharmacokinetic.

[a] If PK samples cannot be processed within the specified time after collection, the PK samples may be collected on the next business day. For all PK samples, the actual date and exact timing (24-hour clock) of PK sample collection and the date, time, and dosage amount of the last 2 doses prior to the PK sample should be recorded.

PK samples must be collected each time the baricitinib dose is increased. If a patient has an adequate response to treatment at a lower dose than the maximum dose, but becomes unresponsive at a later time, the schedule of dose increases and PK sampling can be resumed. If a patient's daily dose is divided into multiple doses, an additional PK sample may be collected pre-dose for each additional dose. For example, a CANDLE patient receiving twice daily dosing who has their total daily dose divided into 3 doses may have a pre-dose PK sample collected before each of the three doses. Additional PK samples may be collected with Sponsor approval to assess safety and dosing.

For all PK samples taken, the actual date and exact timing (24-hour clock) of PK sample collection and the date and time of the last 2 doses prior to the PK sample should be recorded.

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

If the blood volumes required for PK sampling exceed established local guidelines for phlebotomy, then the PK sample collection may be modified.

10.4. Appropriateness of Measurements

The use of the diary score as one of the measurements of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in autoinflammatory conditions conducted by investigators at the National Institutes of Health.

11. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, 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 eCRF data and use standard computer edits to detect errors in data collection

In addition, Lilly or its representatives may 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.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the Sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

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

eCRF data will be encoded and stored in a clinical trial database.

Any data for which paper documentation provided by the patient or parent 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 or parent may include, for example, a paper diary to collect patient-reported outcome measures (for example, a rating scale), a daily dosing schedule, or an event diary.

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Because this study of baricitinib is designed for compassionate use and the conditions being treated are rare, there is no minimum or maximum requirement of the number of patients to be studied.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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, data listings will be the main tool 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.

12.2.2. Patient Disposition

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

12.2.3. Patient Characteristics

A summary and list of demographic information and baseline characteristics of all enrolled patients will be created. Special care will be taken not to include sensitive personal health information that may reveal the identity of the patients.

12.2.4. 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.

12.2.5. Primary Outcome and Methodology

The primary data presentation will be a summary of the percent of patients achieving a decrease in the appropriate diary score by indication. Summaries and by-patient listings of the baseline and final steroid doses and displays of changes over time may be created for those patients receiving steroids. No formal statistical test of any hypothesis will be conducted.

12.2.6. Efficacy

By-patient listings, or summaries where applicable, including the maximum baricitinib dose received by the patient, the maximum decrease in daily corticosteroid dose for those patients receiving steroids at baseline, and the minimum patient diary score achieved while receiving the maximum baricitinib dose, the reason for discontinuation, or the nature of AEs deemed possibly related to investigational product that were experienced by the patient will be created.

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

12.2.6.1. Pharmacokinetic/Pharmacodynamic Analyses

Population PK analysis will be conducted to characterize PK in patients with CANDLE and SAVI. Pharmacokinetic/pharmacodynamic analyses or other analyses may also be conducted if deemed appropriate.

12.2.7. 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.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient or parent understands the potential risks and benefits of participating in the study, including answering any questions the patient or parent may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient or parent in simple terms before the patient is entered into the study, and to document that the patient or parent is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of investigational product.

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 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 majority 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.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonization guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

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 current Investigator's Brochure or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

(1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines

(2) the International Conference on Harmonization GCP Guideline [E6]

(3) applicable laws and regulations

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

All or some of the obligations of the Sponsor may be assigned to a third-party organization.

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.

13.3.1. Investigator Information

Physicians with a specialty in rheumatology with access to hospitals with appropriate pharmacy support and outpatient management will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

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

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

13.3.3. Final Report Signature

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

The Sponsor's responsible medical officer will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol I4V-MC-JAGA Study Schedule

Study Schedule, Protocol I4V-MC-JAGA

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Informed consent		X										
Demographic characteristics		X										
Height		X		X	X	X	X	X	X	X	X	X
Weight		X		X	X	X	X	X	X	X	X	X
Administer tuberculosis test		X[f]										
Read tuberculosis test			X									
Chest x-ray		X[g]										
Electrocardiogram (ECG)		X										
Review inclusion/exclusion criteria		X										
Medical history		X										
Physical examination		X		X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X	X
Assessment of JDM core measures[h]		X										
Vital signs		X		X	X	X	X	X	X	X	X	X
Diary Scores		X		X[i]	X	X	X	X	X	X	X	X
Concomitant medications		X		X	X	X	X	X	X	X	X	X
Preexisting conditions		X										

(continued)

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Adverse events				X	X	X	X	X	X	X	X	X
Investigational drug dose modifications				X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]		
Investigational product returned and compliance assessed					X	X	X	X	X	X		
Laboratory												
Hematology		X		X[l]	X	X	X	X	X	X	X	X
Serum chemistry		X		X[l]	X	X	X	X	X	X	X	X
Fasting lipid panel		X					X	X	X	X	X	X
Urinalysis		X		X[l]	X	X	X	X	X	X	X	X
HBsAg, HBcAb, HBsAb		X[m]										
Hepatitis C antibody		X[m]										
HIV		X[m]										
Thyroid stimulating hormone		X[f]										
BK virus quantitative PCR, plasma		X				X		X	X[t]	X[t]	X	X
BK virus quantitative PCR, urine		X				X		X	X[t]	X[t]	X	X

(continued)

Serum pregnancy test[n]	X										
Urine pregnancy test[n]			X	X	X	X	X	X	X	X	X
Plasma baricitinib concentration[o]			X	X	X	X	X	X	X		
Pulmonary function tests (SAVI patients only)[p]	X		X	X	X	X	X	X	X	X	X

Abbreviations: ET = early termination; JDM = juvenile dermatomyositis; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibiody; HBsAb = hepatitis B surface antibody; HIV = human immunodeficiency virus; SAVI = STING-associated vasculopathy with onset during infancy.

a Early termination visit is required if early termination occurs.
b Visits occur at approximately 4-week intervals during Weeks 16 through 52 (including both required and optional visits)
c Visits occur at approximately 12-week intervals during Weeks 60 through 288.
d Visit 2 encompasses the initial dosing period and can vary in time depending on whether the patient progresses through the first and second dose escalation during this period. Four days is the minimum time.
e Every effort should be made to schedule patient visits within the allowable visit window; however, if a patient visit is scheduled outside the visit window, it will not be considered a protocol violation.
f If results are available from testing within 1 month, then the patient will not have to be retested.
g If a chest x-ray has not been performed in the 6 months prior to screening visit.
h Juvenile dermatomyositis patients only.
i At least 2 consecutive weeks of diary scores are required prior to beginning investigational product.
j Each time study dose is adjusted during Visit 2, this eCRF will be completed.
k See dose escalation schedule (Table JAGA.7.1). Each time study dose is adjusted, this eCRF will be completed. Samples for chemistry, hematology, and urinalysis may be collected 2 weeks after final dose increase. Collect pharmacokinetic samples as described in Section 10.3.2.
l Collect prior to each dose escalation. Investigator will review to ensure dose escalation is appropriate.
m If results are available from testing within the previous 3 months, then the patient will not have to be retested.
n 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 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
o Baricitinib concentration samples will be collected as described in Section 10.3.2. Samples will be collected after Visit 2 if patient has a dose escalation (see Table JAGA.7.1) or as needed for safety monitoring in patients with eGFR < 120 mL/min/1.73 m^2.
p Pulmonary function tests are required for SAVI patients only. Pulmonary function tests may include vital signs, pulse oximetry, imaging, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide. During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased.
q These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2.
r Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained locally.
s Optional physical exams may be performed as needed to document clinically active disease, i.e. rash, fever, arthritis, worsening of splenomegaly, hepatomegaly, and corticosteroid side effects i.e. increase in abdominal girth, cataracts, vertebral fractures due to osteoporosis, Cushinhgoid habitus, substantial weight gain, avascular necrosis, dyslipidemia, hypertension, opportunistic infections or stunted growth, hirsutism, acanthosis nigricans and others.
t BK virus testing required only at on-site, required visits.

Attachment 2. Protocol I4V-MC-JAGA Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b,c]	**Serum Chemistry**[a,b]
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin[c]
Mean cell volume (MCV)	Direct bilirubin[c]
Mean cell hemoglobin concentration (MCHC)	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT/SGPT)[c]
Reticulocyte	Aspartate aminotransferase (AST/SGOT)[c]
Absolute counts of:	Blood urea nitrogen (BUN)[c]
Neutrophils, segmented	Creatinine[c]
Neutrophils, juvenile (bands)	Calcium
Lymphocytes	Glucose
Monocytes	Albumin
Eosinophils	Total protein
Basophils	Creatine phosphokinase (CPK)
Platelets	Uric acid
	Gamma glutamyl transferase (GGT)
	Aldolase[d]
Lipid[e]	
Total cholesterol (TC)	
Low-density lipoprotein (LDL)	
High-density lipoprotein (HDL)	**Other Tests**[a]
Triglycerides	Hepatitis B Surface antigen (HBsAg)[g]
	Anti-Hepatitis B Core antibody (HBcAb)[g]
Urinalysis[a,b,f]	Hepatitis B Surface antibody (HBsAb)[g]
	Hepatitis B Virus DNA[g]
Specific gravity	Human immunodeficiency virus (HIV)[g]
pH	Hepatitis C antibody[h]
Protein	Thyroid-stimulating hormone (TSH)[g]
Glucose	Thyroxine (T4)[g]
Ketones	Pregnancy Test[i]
Bilirubin	QuantiFERON®-TB Gold[g,j]
Urobilinogen	Baricitinib serum concentration
	BK virus quantitative PCR, plasma
	BK virus quantitative PCR, urine
	Urine cytology[f]
	eGFR
Blood	
Leukocyte esterase	
Nitrite	

Abbreviations: PPD = purified protein derivative; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis; WBC = white blood cells.

Footnotes on next page.

a Assayed by local clinical laboratory.
b Unscheduled blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator.
c If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2.
d Perform if inflammatory myositis is present.
e Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to test.
f Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.
g Test required at Visit 1 only to determine eligibility of patient for the study.
h A positive hepatitis C antibody result will be confirmed with a positive hepatitis C virus result.
i For all women of childbearing potential, a serum pregnancy test will be performed at Visit 1 and a urine pregnancy test (local laboratory) will be performed at Visit 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
j The QuantiFERON®-TB Gold 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. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

Attachment 3. Protocol I4V-MC-JAGA Recommended Hepatic Evaluation Guidance Document

Clinical laboratory investigation is highly recommended for diagnosis and monitoring based on the following recommendations adapted from the Drug Induced Liver Injury Guidance published by the FDA in July 2009. Investigators are encouraged to use clinical judgment and may consult with the Lilly clinical research physician for further clarification as necessary.

If an isolated elevation in ALT/AST ≥3 times and ≤5 times ULN or total bilirubin ≥2 times ULN occurs, the patient should be closely observed, including:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the investigational product has been discontinued and the patient is asymptomatic. Monitor AST, ALT, total bilirubin, and alkaline phosphatase until aminotransferase enzymes (ALT, AST) return to <3 times ULN and total bilirubin level <2 times ULN.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases, including history of liver abnormalities or disease (for example, Gilbert's disease) in the patient's family
- Obtaining a history of recent concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtaining a history of exposure to environmental chemical agents (for example, occupational or recreational exposure)
- Obtaining additional tests to evaluate liver function, as appropriate (for example, international normalized ratio, direct bilirubin)
- Consider obtaining gastroenterology or hepatology consultations

In patients with JDM, elevations in ALT/AST up to 5 times ULN may be determined to be myositis-related, subject to the results of additional investigations and clearly stated independent expert opinion, as described in exclusion criterion 31, Section 8.3.2.

If an isolated elevation in ALT/AST >5 times ULN, perform all of the above and obtain gastroenterology or hepatology consultation.

Attachment 4. Protocol I4V-MC-JAGA Patient Diaries

CANDLE and CANDLE - Related Diary

Date of last clinic visit: _____ **Study #:** _____ **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column.

Total Daily Dose _____ **(mg)**

Dose breakdown _____ **(mg)**

Dose Frequency - circle or check one. (number of doses per day)

If your dose or dose frequency changes, start a new diary page starting with the current calendar day.

- 1 time per day ☐
- 2 times per day ☐
- 3 times per day ☐
- 4 times per day ☐
- 5 times per day ☐

0 = No fever	**0** = No rash	**0** = No pain	**0** = No headache	**0** = No fatigue
1 = Fever without impact on daily activity	**1** = Rash barely present	**1** = Mild pain not requiring medication, no limping	**1** = Mild headache not requiring medication or any adjustments of daily activities	**1** = Mild fatigue, no functional impact
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	**2** = Rash covering 10% of body surface area	**2** = Pain requiring medication or leading to limping or other mild functional impact	**2** = Headache requiring medication or having mild functional impact	**2** = Moderate fatigue with mild functional impact
3 = Fever requiring medication with significant impact on daily activities (missing school, listlessness)	**3** = Rash covering more than 30% of body surface area	**3** = Pain requiring medication or having a severe functional impact	**3** = Headache requiring medication and having a severe functional impact	**3** = Severe fatigue with a severe functional impact
4 = Fever forcing the patient to be bedridden	**4** = Worst rash ever or covering over 30% of body surface area or hurting or stinging	**4** = Severe pain, child refusing to walk, or staying in bed most of the time	**4** = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	**4** = Severe fatigue resulting in patient staying in bed most of the time

Day	Date MM/DD/YYYY	Total Daily Dose JAGA (mg) Given	Missed JAGA Dose (mg) & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Dose of Steriods (mg)	Name or initials of person entering information, each day
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
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26											
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28											
29											
30											
31											

NIH Study Team

Reviewer Name: _____ Reviewer Signature: _____ Date Reviewed: _____

JDM Diary

Date of last clinic visit: _____ **Study #:** _____ **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

Total Daily Dose _____ **(mg)**

Dose breakdown _____ **(mg)**

Dose Frequency - circle or check one. (number of doses per day)

If your dose or dose frequency changes, start a new diary page starting with the current calendar day.

- 1 time per day ☐
- 2 times per day ☐
- 3 times per day ☐
- 4 times per day ☐
- 5 times per day ☐

0 - No fever	0 - No rash	0 - No pain	0 - No headache	0 - No fatigue	0 - No muscle
1 - Fever without impact on daily activity	1 - Rash barely present	1 - Mild pain not requiring medication, no limping	1 - Mild headache not requiring medication or any adjustments of daily activities	1 - Mild fatigue, no functional impact	1 - Mild weakness
2 - Fever requiring fever-reducing medication or with mild impact on daily	2 - Rash generally brighter pink to red	2 - Pain requiring medication or leading to limping or other mild functional	2 - Headache requiring medication or having mild functional impact	2 - Moderate fatigue with mild functional impact	2 - Moderate weakness
3 - Fever requiring medication with significant impact on daily activities (missing school	3 - Rash generally bright red	3 - Pain requiring medication or having a severe functional impact	3 - Headache requiring medication and having a severe functional impact	3 - Severe fatigue with a severe functional impact	3 - Severe weakness
4 - Fever forcing the patient to be bedridden	4 - Worst rash ever	4 - Severe pain, child refusing to walk, or staying in bed most of the time	4 - Severe headache resulting in patient staying in bed most of the day or lying down due to headache	4 - Severe fatigue resulting in patient staying in bed most of the time	4 - Extremely severe weakness

Day	Date MM/DD/YYYY	Total Daily Dose JAGA mg Given	Missed JAGA Dose & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Weakness	Dose of Steroids (mg)	Name or initials of person entering information, each day
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
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20												
21												
22												
23												
24												
25												
26												
27												
28												
29												
30												
31												

Key for scoring per symptom:

Fever	0 - As listed above
Rash	0 - no rash
	1 - Faint pink - involvement of a smaller area, such as joints, eyelids, and/or cheeks
	2 - Pink to red - involvement of moderate area, such as joints, face, hands, and arms,
	3 - Bright red - often with more extensive involvement of moderate area, such as joints, face, neck & shoulders, hands & arms, lower extremities, & possibly trunk or
	4 - Worst - Extremely bright red & often with itchiness, scratching, or with
Musculoskeletal	0 - As listed above
Headache	0 - As listed above
Fatigue	0 - As listed above
Weakness	0 - No weakness - Strong in all muscle groups & have no problems with their muscle strength or ability to do things compared to their peers
	1 - Mild Weakness - Almost normal strength in all muscles & can do almost everything with their muscles that their peers can do with minimal/mild problems
	2 - Moderate Weakness - Their muscles are somewhat weak; can do things with their muscles, but wring their muscles for many things is hard for them)
	3 - Severe Weakness - Their muscles are very weak & wring their muscles for most things is hard for them; they need assistance with some things)
	4 - Extremely Severe Weakness - Their muscles are extremely weak & wring their

MIH Study Team

Name: _____

Reviewer Signature: _____

Date Reviewed: _____

SAVI Diary

Date of last clinic visit: _____ **Study #:** _____ **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

Total Daily Dose _____ **(mg)**

Dose breakdown _____ **(mg)**

Dose Frequency - circle or check one. (number of doses per day)

If your dose or dose frequency changes, start a new diary page starting with the current calendar day.

- 1 time per day ☐
- 2 times per day ☐
- 3 times per day ☐
- 4 times per day ☐
- 5 times per day ☐

	0 - No fever	0 - No rash	0 - No pain	0 - No fatigue	0 - No breathing problems	0 - No ulcers
	1 - Fever without impact on daily activity	1 - Rash barely present	1 - Mild pain not requiring medication, no limping	1 - Mild fatigue, no functional impact	1 - Mild breathing problems / rapid breathing / coughing, no functional impact	1 - Few ulcers, only in 1 location and/or no drainage, no ischemia
	2 - Fever requiring fever-reducing medication or with mild impact on daily activity	2 - Rash covering 10% of body surface area	2 - Pain requiring medication or leading to limping or other mild functional impact	2 - Moderate fatigue with mild functional impact	2 - Moderate breathing problems / rapid breathing / coughing with mild functional impact	2 - Ulcers in more than 1 location and/or with some drainage, no ischemia
	3 - Fever requiring medication with significant impact on daily activities (missing school, bed/nurses)	3 - Rash covering more than 30% of body surface area	3 - Pain requiring medication or having a severe functional impact	3 - Severe fatigue with a severe functional impact	3 - Severe breathing problems / rapid breathing / coughing with a severe functional impact	3 - Ulcers in multiple locations and/or significant drainage, and/or any ischemia
	4 - Fever forcing the patient to be bedridden	4 - Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 - Severe pain, child refusing to walk, or staying in bed most of the time	4 - Severe fatigue resulting in patient staying in bed most of the time	4 - Severe breathing problems / rapid breathing / coughing which result in patient staying in bed most of the time	4 - Severe ulcers / ischemic lesions in multiple locations

Day	Date MM/DD/YYYY	Total Daily JAGA Dose Given (mg)	Missed JAGA Dose & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Fatigue	Respiratory/ Breathing Symptoms	Ulcers / Ischemic lesions	Dose of Steriods (mg)	Peak Flows	Name or initials of person entering information, each day
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
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NIH Study Team

Name:_____ Reviewer Signature: _____ Date Reviewed: _____

Attachment 5. Protocol I4V-MC-JAGA Bohan and Peter Criteria for the Diagnosis of Polymyositis and Dermatomyositis

Criteria for the Diagnosis of Polymyositis and Dermatomyositis[a]

Criterion	Definition
1. Symmetrical Weakness	Weakness of proximal muscles
2. Muscle Biopsy Evidence	Evidence of necrosis of Type I and II fibers: degeneration and regeneration of myofibers with variation in myofiber size; or focal collections of interstitial or perivascular mononuclear cells
3. Elevation of Muscle Enzymes	Elevation in serum of a skeletal muscle enzyme, particularly creatine phosphokinase, aldolase, aspartate aminotransferase (SGOT or AST), alanine aminotransferase (SGPT or ALT), or lactate dehydrogenase (LDH)
4. Electromyographic Evidence	Short duration, small, low amplitude polyphasic potentials; fibrillation potentials, seen even at rest; or bizarre, high-frequency, repetitive discharges
5. Dermatologic Features	Scaly erythematous palpable erythematous eruptions of the metacarpophalangeal or interphalangeal joints, knees, elbows, or medial malleoli (Gottron's papules); erythematous macules over the m metacarpophalangeal or interphalangeal joints, knees, elbows, or medial malleoli (Gottron's sign); or periorbital or upper eyelid purplish discoloration (heliotrope rash)

[a] Confidence limits can be defined as follows: For a definite diagnosis of dermatomyositis, 3 of 4 criteria plus the rash must be present. For a probable diagnosis of dermatomyositis, 2 criteria plus the rash must be present. For a possible diagnosis of dermatomyositis, 1 criterion plus the rash must be present.

Data from Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med.* 1975;292(7):344–347, with permission, as modified by the International Myositis Assessment and Clinical Studies Group [Oddis CV, Rider LG, Reed AM, Ruperto N, Brunner HI, Koneru B, Feldman BM, Giannini EH, Miller FW, International Myositis A, Clinical Studies G. International consensus guidelines for trials of therapies in the idiopathic inflammatory myopathies. *Arthritis Rheum.* 2005;52(9):2607-15].

Attachment 6. Protocol I4V-MC-JAGA Juvenile Dermatomyositis Core Set Measures

Core Set Measures

Domain	Core Set Measures
Global Activity	Physician global disease activity assessment by Likert or VAS Parent/patient global disease activity assessment by Likert or VAS
Muscle Strength	MMT by a 0 to 10 point or expanded 0 to 5 point scale to include proximal, distal, and axial muscles (adults and children ≥4 years of age)
Physical Function	Validated parent/patient questionnaire of activities of daily living (HAQ/CHAQ)
Laboratory Assessment	Activity of at least one serum muscle enzyme from the following: creatine kinase (CK), aldolase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)
Extramuscular Disease	A validated approach that is comprehensive and assesses cutaneous, gastrointestinal, articular, cardiac, and pulmonary activity. Myositis Disease Activity Assessment Tool has been validated.

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; HAQ = Health Assessment Questionnaire; MMT = Manual Muscle Test – 8 designated muscles; VAS = visual analog scale.

Manual Muscle Testing – 8 Designated Muscles

Muscle Groups	Right (0 – 10)	Left (0 – 10)	Axial (0 – 10)
Axial Muscles (0 – 10)			
Neck Flexors	—	—	0 – 10
Proximal Muscles (0 – 100)			
Deltoid	0 – 10	0 – 10	—
Biceps brachii	0 – 10	0 – 10	—
Gluteus maximus	0 – 10	0 – 10	—
Gluteus medius	0 – 10	0 – 10	—
Quadriceps	0 – 10	0 – 10	—
Distal Muscles (0 – 40)			
Wrist extensors	0 – 10	0 – 10	—
Ankle dorsiflexors	0 – 10	0 – 10	—
MMT-8 Score (0 – 150)	0 – 70	0 – 70	0 – 10

Abbreviations: MMT = Manual Muscle Test – 8 designated muscles.

Attachment 7. Protocol I4V-MC-JAGA Myositis Patient/Parent Global Activity Assessment

IMACS FORM 03: PATIENT/PARENT GLOBAL ACTIVITY ASSESSMENT

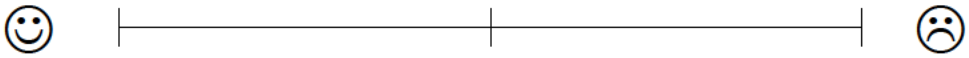
Assessor _____

Assessor's relationship to subject: Patient__; Mother:__; Father__; Other (specify):_____

Date of assessment (mm/dd/yy) _____

Your myositis is the result of the combined effects of many disease processes. One of these is disease activity, which is active inflammation in your/your child's muscles, skin, joints, intestines, heart, lungs or other parts of your body, which can improve when treated with medicines.

1. Considering all the ways that myositis affects you/your child, please rate the overall activity of your/your child's disease today by placing a mark on the line below.



No evidence of disease activity

Extremely active or severe disease activity

Attachment 8. Protocol I4V-MC-JAGA Myositis Physician's Global Activity Assessment

IMACS FORM 02: PHYSICIAN GLOBAL ACTIVITY ASSESSMENT

Assessor _____

Date of assessment (mm/dd/yy) _____

Physician Global Activity Assessment

Disease Activity is defined as potentially reversible pathology or physiology resulting from the myositis. Clinical findings known or suspected to be due to another disease process should not be considered in this evaluation. The global assessment of disease activity is to be judged from all the information available to you today including the subject's appearance, history, physical examination, diagnostic laboratory testing and your resultant medical therapy.

Please rate your global (overall) disease activity assessment by drawing a vertical mark on the 10-cm. line below according to the following scale: left end of line = no evidence of disease activity, midpoint of line = moderate disease activity, and right end of line = extremely active or severe disease activity.

No evidence of disease activity — Extremely active or severe disease activity

Also rate global disease activity on a 5-point Likert scale:

___0 = none
___1 = mild activity
___2 = moderate activity
___3 = severe activity
___4 = extremely severe activity

Attachment 9. Protocol I4V-MC-JAGA Myositis Disease Activity Assessment Tool

IMACS FORM 07a: Modified MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL – 2005, Version 2

ASSESSOR: _____ **Date Assessed:** _____

General Guidelines for Completion:

Please rate your overall (global) assessment of the ongoing **extramuscular** disease activity over the past 4 weeks on the 0-10cm VAS scale by drawing a **vertical** mark on the 10cm line according to the following guidelines:

- left end of line = no evidence of disease activity
- midpoint of line = moderate disease activity
- right end of line = extreme or maximum disease activity

* Clinical findings known or suspected to be due to another disease process or due to therapy should **NOT** be considered in this evaluation
* Disease activity is defined as a potentially reversible finding.
* Myositis or muscle disease activity should be excluded from this assessment.

Extramuscular Global Assessment	**(Absent)** ——— **(Maximum)** __ __ . __ cm	Overall evaluation for disease activity in all extramuscular systems **(EXCLUDING MUSCLE DISEASE ACTIVITY)**

Attachment 10. Protocol Amendment I4V-MC-JAGA(u) Summary
Compassionate Use Treatment Protocol I4V-MC-JAGA(u): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Overview

Protocol I4V-MC-JAGA has been amended. The new protocol is indicated by amendment (u) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Increased the number of patients allowed to be enrolled due to investigator feedback on planned patient enrollment through the planned enrollment cut-off date.

Revised Protocol Sections

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

Cover Page

Study I4V-MC-JAGA is an open-label compassionate use treatment program to provide baricitinib to patients with conditions expected to benefit from JAK inhibition: CANDLE, CANDLE-related conditions, SAVI, and severe juvenile dermatomyositis. Patients will receive an initial dose based on their weight class and eGFR that may be escalated to determine a tolerable dose. Patients may be dosed for up to 288 weeks. It is anticipated that up to ~~60~~ 85 patients may be treated with baricitin b in an individualized manner. The treatment guidelines contained herein are for compassionate use only. Within these guidelines, open-label baricitinib will only be administered to patients who meet inclusion and exclusion criteria.

Synopsis: Study I4V-MC-JAGA

Number of Planned Patients/Subjects: Entered: up to ~~60~~85 Enrolled: up to ~~60~~85 Completed: up to ~~60~~85	**Phase of Development:** Not Applicable for Compassionate Use

Leo Document ID = 2f2ca89d-949d-40b8-8a2b-c5660cbe15e4

Approver: PPD
Approval Date & Time: 08-Aug-2018 14:14:22 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 08-Aug-2018 14:14:22 GMT
Signature meaning: Approved

1. Protocol Addendum I4V-MC-JAGA (3.3) Compassionate Use Treatment Protocol I4V-MC-JAGA(u): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Baricitinib (LY3009104)

This addendum is to be performed in addition to all procedures required by protocol I4V-MC-JAGA(u) or any subsequent amendments to that protocol.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Addendum (3) Electronically Signed and Approved by Lilly on 22-Oct-2015.
Revised Protocol Addendum (3.1) Electronically Signed and Approved by Lilly on 09-Sep-2016.
Revised Protocol Addendum (3.2) Electronically Signed and Approved by Lilly on 15-May-2018.
Revised Protocol Addendum (3.3) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 08-Aug-2018 GMT

2. Table of Contents

Protocol Addendum I4V-MC-JAGA (3.3) Compassionate Use Treatment Protocol I4V-MC-JAGA(u): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Section **Page**

List of Attachments

Attachment **Page**

3. Rationale for Addendum

This addendum applies to sites enrolling patients with Aicardi-Goutières Syndrome (AGS). AGS is a monogenic disorder resulting from loss-of-function 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). Given that AGS is an interferon-mediated disease, patients with AGS are expected to benefit from JAK1 and JAK2 inhibition and, thus, it may be beneficial to treat them with baricitinib. The purpose of this addendum is to add specific entry and patient assessment criteria for patients with AGS to the existing Protocol I4V-MC-JAGA(u). This addendum is being revised in order to specify additional considerations and procedures for patients <6 months of age with AGS.

4. Protocol Additions

The following sections of Protocol I4V-MC-JAGA(u) have been modified in this addendum to allow patients with AGS to be eligible for enrollment at specific sites.

2. Synopsis

Number of Planned Patients/Subjects: Entered: up to 85 Enrolled: up to 85 Completed: up to 85
Objectives: The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, juvenile dermatomyositis (JDM), SAVI, or AGS results in a reduction in the patient's mean daily diary scores as follows: • CANDLE diary: reduction in mean daily score to <0.5 • SAVI diary: reduction in mean daily score to <1.0, exclusive of respiratory/breathing symptom, and a <1.0 increase from baseline in the respiratory/breathing symptom • JDM diary: reduction in mean daily score exclusive of fever and headache symptoms by ≥0.25 • AGS diary: reduction in mean daily score to <0.5.
Diagnosis and Main Criteria for Inclusion and Exclusions: Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder for which there is reason to believe that JAK 1/2 inhibition will be beneficial. One such autoinflammatory disorder is chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. CANDLE syndrome 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). Other patients eligible to be enrolled into this study include those diagnosed with conditions related to CANDLE syndrome involving immune dysregulation: stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), an autoinflammatory syndrome with interferon (IFN) pathway dysregulation, juvenile dermatomyositis (JDM), and Aicardi-Goutières syndrome (AGS).

5. Introduction

The purpose of this open-label, compassionate use, treatment protocol is to provide baricitinib to patients with CANDLE*, CANDLE-related conditions, SAVI,* severe juvenile dermatomyositis (JDM), and Aicardi-Goutières syndrome (AGS) who are not responsive to biologic therapies and who require treatment with high doses of steroids to control systemic signs and symptoms of their condition (or, in the opinion of the investigator, have failed an adequate course of steroids or are not suitable candidates for steroid treatment, such as patients with a confirmed genetic diagnosis of CANDLE or SAVI) and are eligible for treatment under this protocol. Baricitinib is an orally administered inhibitor of Janus kinases 1 and 2 (JAK1 and JAK2).

Autoinflammatory Diseases

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

- **Aicardi-Goutières Syndrome (AGS).** 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 (for example, glaucoma, cardiomyopathy, neuropathy, endocrinological problems) in many patients. All available literature sources suggest that the prevalence of AGS is well below 5 in 10,000 persons.

Most 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 in any of the genes encoding the DNA exonuclease TREX1 (TREX1), the three non-allelic components of the RNase H2 endonuclease complex (RNASEH2A, RNASEH2B, and RNASEH2C), the deoxynucleoside triphosphate triphosphohydrolase SAMHD1 (SAMHD1), the double-stranded RNA editing enzyme ADAR (ADAR), and the double-stranded RNA cytosolic sensor IFIH1/MDA5 (IFIH1).

The proteins defective in AGS are all associated with nucleic acid metabolism/sensing. It is hypothesized that six of these proteins are involved in limiting the accumulation (TREX1, the three RNase H2 complex components, SAMHD1), or the nature (ADAR), of intracellular nucleic acid species, a failure of which process 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 interferon-stimulatory nucleic acids, and offers an elegant mechanistic explanation for the phenotypic overlap of AGS with congenital infection and systemic lupus erythematosus (SLE). 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 interferon alpha-mediated immune response and, sometimes, the production of antibodies against self-nucleic acids.

AGS is associated with increased levels of interferon alpha in the cerebrospinal fluid (CSF) and serum. However, interferon alpha levels, and white cell counts, in the CSF 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 CSF sampling, very few serial data are available

(that is, systematic interferon alpha activity profiling beyond infancy has not been undertaken). Indeed, data acquired more recently on more than 200 AGS patients using qPCR analysis of interferon stimulated genes (ISGs) indicates the presence of a so-called "interferon signature" at any age in almost 100% of patients with mutations in TREX1, RNASEH2A, RNASEH2C, SAMHD1, ADAR, and IFIH1. Around 30% of patients with RNASEH2B mutations demonstrated no such upregulation—but as ISG sampling in these studies was usually performed many years after initial diagnosis, it remains possible that all patients exhibit a positive interferon 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 life-long in most patients.

Although some children are affected by the time of birth (that is, the disease has an in utero onset), most experience the onset of disease at some point post-natally, 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, for example, 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 here, 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 interferons can have a neurotoxic effect at the cellular level in the absence of obvious neuroimaging changes. Most recently, IFIH1 gain-of-function 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.

Summary

Patients with CANDLE, CANDLE-related conditions, SAVI, severe JDM, and AGS who are not responsive to at least 1 biologic therapy (except as noted in the inclusion/exclusion criteria), and who require treatment with oral corticosteroids (≥0.15 mg/kg/day of prednisone or its equivalent) to control systemic signs and symptoms of their syndrome (or, in the opinion of the investigator, have failed an adequate course of steroids, except as noted in the inclusion/exclusion criteria), will be candidates for baricitinib treatment. 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 CANDLE, CANDLE-related conditions, SAVI, severe JDM, and AGS for whom biologics have proven to be ineffective and/or there are no other treatments, thereby offering these patients an alternative compassionate use therapeutic option.

6. Objectives

6.1. Primary Objective

The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, JDM, or AGS results in reduction in the patient's mean daily diary scores as follows:

- CANDLE diary: reduction in mean daily score to <0.5
- SAVI diary: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and respiratory/breathing symptoms score a <1.0 increase from baseline
- JDM diary: reduction in mean daily score exclusive of fever and headache symptoms by ≥0.25
- AGS diary: reduction in mean daily score to <0.5.

7. Investigational Plan

7.1. Summary of Study Design

Screening, Initial Treatment, and Dose Escalation:

Baricitinib will be dosed by patient weight range and eGFR. See Table JAGA.7.1 for the dosing schedule for patients with eGFR ≥120 mL/min/1.73 m^2 or normal eGFR for patients age <17.5 months. AGS patients <6 months old and <8.5 kg may receive an initial dose of 0.5 mg BID provided that renal function based on eGFR is within normal range for age as documented by an expert independent of the principal investigator (preferably a neonatologist or pediatric nephrologist). Dosing in younger children <8.5 kg in weight was determined by extrapolating the mg/kg dose from older patients weighing at least 8.5 kg (i.e. initial dose of ~0.2 mg/kg). If tolerated, the dose may be increased to 1 mg BID as shown in Table JAGA.7.1. Tolerance will be judged by stability or improvement in hematology and chemistry laboratory test results collected as specified in Protocol Attachment 1 (Study Schedule) and section 10.2.2.2 below. Once the patient is >6 months old the dose may be increased as specified in Table JAGA.7.1. When clinically indicated, smaller dose increments than specified in Table JAGA.7.1 may be used. Dose increases other than specified in Table JAGA.7.1 may be considered after consultation and agreement with the Sponsor.

See Table JAGA.7.2 for the dosing schedule for patients with eGFR <120 mL/min/1.73 m^2 or patients <17.5 months with abnormal eGFR (40-60 mL/min/1.73 m^2). Patients ≥6 months and <17.5 months with weight in the range of 4.5 to <8.5 kg, and an eGFR of 40-60 mL/min/1.73 m^2 may receive an initial dose of 0.5 mg BID. This dose should not be increased until the patient has an eGFR >60 mL/min/1.73 m^2 (as shown in Table JAGA.7.1) or until the patient is at least

17.5 months old and weighs at least 8.5 kg (as shown in Table JAGA.7.2), or after consultation and agreement with the Sponsor.

Continuing Treatment: After the patient has received baricitinib at the target dose level for approximately 14 days, the patient will have an evaluation performed, which will include an assessment of the patient's clinical condition, AEs, and blood tests for safety per the Study Schedule. Safety laboratory assessments will be performed and reviewed by the investigator along with a copy of the patient's diary. AEs and concomitant medications will be assessed over the phone or in person by the study team. Once the patient has reached a stable dose of baricitinib, the same total dose may be administered as equal or unequal divided doses (administered up to 4 doses in a day [24 hours]). If more than 4 doses are needed in 1 day (24 hours), then consultation and agreement with the Sponsor will be required.

1. If the patient is responding adequately to treatment (average diary score <0.5 or <1.0 [CANDLE/AGS or SAVI diaries, respectively] or reduction in average diary score ≥0.25 exclusive of fever and headache symptoms [JDM diary]), the patient will continue receiving baricitinib therapy with follow-up appointments according to the Study Schedule. Steroid weaning may begin for patients who are receiving steroids. If the patient is responding to treatment, but has not met the threshold to begin steroid weaning and is experiencing clinically significant adverse effects from steroids, steroid weaning may begin when, in the opinion of the investigator, an adequate response has been achieved.

5. If a patient reaches the maximum allowable dose (or had a dose modification as described in item 3 above [see Protocol I4V-MC-JAGA(u)]) and his or her average diary score has decreased, but has not met the threshold for adequate response/steroid weaning (does not reach an average diary score of <0.5 or <1.0 [CANDLE/AGS or SAVI diaries, respectively] or does not achieve a reduction in the average diary score by ≥0.25 exclusive of fever and headache symptoms [JDM diary]), the patient may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment.

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 (that is, CANDLE, JDM, SAVI, or AGS). The assessments included in the patient diaries are shown in Attachment 1, Attachment 2, and Attachment 3. Each patient (or caregiver) will complete the diary at approximately the same time every day during the screening period and during the duration of the study. Ideally, the same person will complete the diary each day. During clinic visits, it is preferable that the patient or caregiver complete the patient diary rather than site staff. As this protocol will include patients with a spectrum of clinical symptoms, the investigator will determine which features listed in the diary are present and representative of the disease activity for the individual patient. Only these identified features will be used to determine average diary scores as a treatment outcome for the patient.

For patients with CANDLE, SAVI, or JDM, the patient or caregiver will be instructed to rate each symptom (fever, rash, musculoskeletal pain, and fatigue [all diaries], headache [CANDLE and JDM diaries], weakness [JDM 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]). 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. 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.

The diary is to be completed daily throughout the study. The diary score is calculated after approximately 7 to 10 days of therapy at a stable dose to assess disease activity and inform the need for an additional dose increase (up to the maximum allowed dose as detailed in the clinical protocol I4V-MC-JAGA(u)) or initiation of steroid weaning as described (if the patient is receiving steroids). At each visit, the investigator will calculate the average score for each symptom being collected on the diary (that is, the average of the daily scores since the previous visit, correcting for any day for which diary scores were not recorded). The investigator 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. An average diary score ≥ 0.5 (CANDLE or AGS diary) or ≥ 1.0 (SAVI diary) or a reduction in the average diary score of <0.25 exclusive of fever and headache symptoms (JDM diary), or ongoing clinical disease activity reflected by increased symptoms not captured on the diary will be indicative of a lack of complete response and will trigger a dose escalation. An average diary score <0.5 (CANDLE or AGS diary) or <1.0 (SAVI diary) or a reduction in the average diary score ≥ 0.25 exclusive of fever and headache symptoms (JDM diary) will be indicative of a response to treatment and will trigger initiation of steroid weaning (if the patient is receiving steroids). The investigator should review the entire diary and diary score at each appropriate interval. If there is a trend in the diary scores, (that is, initial high scores resolve by the end of the diary period), the investigator has the option of escalating or not escalating the patient's dose of baricitinib.

Patients whose average diary scores decrease after receiving the maximum allowable dose level of baricitinib (as defined in the clinical protocol I4V-MC-JAGA(u)), but do not meet the threshold for steroid weaning (for patients receiving steroids at baseline), or an adequate response (do not reach an average daily CANDLE or AGS diary score <0.5 or SAVI diary score <1.0), or do not achieve a reduction in the JDM diary score of ≥ 0.25 exclusive of fever and headache symptoms), may continue in the study if the investigator determines that it is in the

best interest of the patient to continue treatment. This will not be considered to be a protocol violation.

Table JAGA.7.1. Dose Escalation Schedule for Patients with eGFR ≥120 mL/min/1.73 m^2 or Normal eGFR for Age <17.5 Months

Initial Dose

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
Weight: 4.5 to <8.5 kg, Age: <6 months	Normal for age <6 months	0.5 mg	—	0.5 mg	1 mg	Based on tolerability	0.12/0.22	BID
Weight: 4.5 to <8.5 kg, Age: ≥6 to <17.5 months	>60 (normal for age range)	1 mg	—	1 mg	2 mg	72 hours	0.24/0.44	BID
Weight: 8.5 to <20 kg Age: ≥17.5 months	≥120	2 mg	2 mg	2 mg	6 mg	72 hours	0.3/0.71	TID
20-40 kg	≥120	3 mg	—	3 mg	6 mg	72 hours	0.15/0.3	BID
>40 kg	≥120	4 mg	—	4 mg	8 mg	72 hours	NA/0.2	BID

First Dose Escalation

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
Weight: 4.5 to <8.5 kg, Age: <6 months	Normal for age <6 months	1 mg	—	1 mg	2 mg	NA	0.24/0.44	BID
Weight: 4.5 to <8.5 kg, Age: ≥6 to <17.5 months	>60 (normal for age range)	2 mg	—	2 mg	4 mg	72 hours	0.47/0.89	BID
Weight: 8.5 to <20 kg Age: ≥17.5 months	≥120	2 mg	2 mg 2 mg	2 mg	8 mg	72 hours	0.4/ 0.94	QID
20-40 kg	≥120	3 mg	2 mg	3 mg	8 mg	72 hours	0.2/0.4	TID
>40 kg	≥120	5 mg	—	5 mg	10 mg	72 hours	NA/ 0.25	BID

Second Dose Escalation (only in patients > 40 kg)

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
>40 kg	≥120	6 mg	—	6 mg	12 mg	72 hours	NA/0.3	BID

Abbreviations: max = maximum; min = minimum; NA = not applicable.
— indicates no further dose escalation allowed.

a See JAGA Protocol amendment(u) Section 9.4 if a change in the patient's weight during the study would place the patient in a different weight range.

b After reaching a stable dose, the total daily dose can be administered as equal or unequal divided doses.

c Duration of treatment prior to escalation includes days to obtain samples and results from safety blood test assessments prior to the first dose or first dose increase.

d Dose in mg/kg for the lowest weight and highest weight in each weight class.

Table JAGA.7.2. Dose Escalation Schedule for Patients with eGFR <120 mL/min/1.73 m^2 or for Patients <17.5 Months with Abnormal eGFR (40-60 mL/min/1.73 m^2)

Initial Dose[a]

Weight Class[b]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
Weight: 4.5 to <8.5 kg, Age: ≥6 to <17.5 months	40-60	0.5 mg	—	0.5 mg	1 mg	72 hours	0.12/0.22	BID
Weight: 8.5 to <20 kg, Age: ≥17.5 months	<120	2 mg	—	2 mg	4 mg	72 hours	0.2/0.47	BID
20-40 kg	<120	2 mg	—	2mg	4 mg	72 hours	0.1/0.2	BID
>40 kg	<120	2 mg	—	2 mg	4 mg	72 hours	NA/0.1	BID

First Dose Escalation (only for patients with eGFR ≥ 60 mL/min/1.73 m^2)

Weight Class[b]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
Weight: 8.5 to <20 kg, Age: ≥17.5 months	60-119	2 mg	2 mg	2 mg	6 mg	72 hours	0.3/0.71	TID
20-40 kg	60-119	3 mg	—	3 mg	6 mg	72 hours	0.15/0.3	BID
>40 kg	60-119	3 mg	—	3 mg	6 mg	72 hours	NA/0.15	BID

a Baricitinib should not be used in patients with eGFR < 30 mL/min/1.73 m^2.

b See JAGA Protocol amendment(u) Section 9.4 if a change in the patient's weight during the study would place the patient in a different weight range.

c Duration of treatment prior to escalation includes days to obtain samples and results from safety blood test assessments prior to the first dose or first dose increase.

d Dose in mg/kg for the lowest weight and highest weight in each weight class.

7.2. Discussion of Design and Control

This compassionate use study is an open-label, single-arm design intended to provide baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, severe JDM, or AGS. Baricitinib has not been investigated in children; therefore, patients will receive an initial dose that may be escalated using dose escalation tables to an effective and tolerable dose. The dose-escalation period allows for safety assessments in between dose escalations. This study, by the nature of compassionate use, is not intended to answer any research hypothesis; however, it is intended to provide a potential treatment for inflammatory conditions proven resistant to other therapies. Though the open-label, single-arm design has potential for the introduction of bias, the study design represents an ethical approach for treatment of these conditions within a compassionate use framework.

8. Study Population

Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder such as CANDLE syndrome, CANDLE-related syndrome, SAVI, or AGS, or will have been diagnosed with severe JDM. CANDLE syndrome clinically presents 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). Failure to thrive and lymphadenopathy and hypochromic or normocytic anemia can be seen (Ramot et al. 2010; Torrelo et al. 2010).

8.1. Inclusion Criteria

2) Have an average daily diary score of ≥0.5 (CANDLE or AGS diary) or ≥1.0 (SAVI diary) or ≥1.0 exclusive of headache and fever symptoms (JDM diary) assessed over at least 2 weeks prior to entry, if available. Otherwise, patients can complete the diary after study consent is signed during the screening period and meet the inclusion criteria for enrollment into the study.

3) Are ≥17.5 months of age (or are ≥6 months of age with AGS). Patients younger than 17.5 months (or 6 months with AGS) of age can be considered for enrollment after discussion with the Sponsor.

5) Have been previously treated with at least 1 biologic therapy and, in the opinion of the investigator, did not respond or are no longer responding to therapy. If the patient has been diagnosed with CANDLE, Nakajo-Nishimura syndrome, SAVI, AGS, or an equivalent syndrome, the need for previous biologic therapy is not required.

6) Require treatment with oral corticosteroids (≥0.15 mg/kg/d of prednisone or its equivalent) for control of systemic signs and symptoms of their chronic inflammatory disease for at least 2 weeks prior to study entry, or in the opinion of the investigator, have failed an adequate course of steroids. Exceptions to this criterion are patients with a confirmed genetic diagnosis of SAVI or CANDLE. Treatment with or failure of treatment with steroids is not required for patients with AGS.

8.1.3. Patients with Aicardi-Goutières Syndrome

Patients with AGS are eligible for entry into the study (that is, eligible to sign consent) only if they meet all of the common inclusion criteria (1 through 8 in Section 8.1 of the Clinical Protocol I4V-MC-JAGA(u)) and the following criterion:

48) A molecular diagnosis of AGS or neuroimaging and clinical findings consistent with a diagnosis of AGS.

8.2. Exclusion Criteria

20) Have been exposed to a live vaccine within 12 weeks prior to entry or are expected to need/receive a live vaccine (including herpes zoster vaccination) during the course of the study. Young patients who are not yet vaccinated and will be unable to receive live vaccines while they are receiving the program drug (baricitinib) may be included after discussion with the Sponsor.

Note: Investigators should review the vaccination status of their patients and follow the local guidelines for vaccination with nonlive vaccines intended to prevent infectious disease prior to entering patients into the study.

23) Have an estimated glomerular filtration rate (eGFR) based on the most recent available serum creatinine of <40 mL/min/1.73 m^2. Normal eGFR in patients <6 months may be <40 mL/min/1.73m^2 and AGS patients younger than 6 months of age with normal eGFR may be enrolled after discussion with the Sponsor.

8.3. Enrollment Criteria

8.3.1. Inclusion Criteria

29) Have a mean daily diary score of ≥0.5 (CANDLE or AGS diary) or ≥1.0 (SAVI diary) or ≥1.0 exclusive of headache and fever symptoms (JDM diary) assessed over at least 2 weeks prior to enrollment, including patients who completed the diary after consent was signed.

8.3.2. Exclusion from Study Enrollment

31) Have any of the following specific abnormalities on screening laboratory tests:
- Hemoglobin <10 g/dL (100 g/L). Patients with CANDLE, CANDLE-related conditions, SAVI, or AGS may be enrolled with hemoglobin <10 g/dL if the anemia is considered a result of the underlying disease (see below).

- Total WBC count <2500 cells/µL. Patients with CANDLE, CANDLE-related conditions, SAVI, or AGS may be enrolled with WBC count <2500 cells/µL if the low WBC count is considered a result of the underlying disease (see below).
- Neutropenia (absolute neutrophil count [ANC] <1200 cells/µL). Patients with CANDLE, CANDLE-related conditions, SAVI, or AGS may be enrolled with an ANC <1200 cells/µL if the low ANC is considered a result of the underlying disease (see below).
- Thrombocytopenia (platelets <100,000/µL). Patients with CANDLE, CANDLE-related conditions, SAVI, or AGS may be enrolled with a platelet count <100,000/µL if the low platelet count is considered a result of the underlying disease (see below).
- eGFR <40 mL/min/1.73 m^2
  Normal eGFR in patients <6 months may be <40 mL/min/1.73m^2 and AGS patients younger than 6 months of age with normal eGFR may be enrolled after discussion with the Sponsor.

Note: A patient with CANDLE, CANDLE-related condition, SAVI, or AGS may be enrolled with any of the above specific abnormalities on screening laboratory tests if these laboratory abnormalities are considered a feature of the disease. An expert independent of the principal investigator (preferably a hematologist) must evaluate the patient and, in conjunction with the principal investigator, document that the laboratory abnormality is a feature of the underlying CANDLE, CANDLE-related condition, or SAVI condition; the investigator must also consult with the Sponsor before the patient can be enrolled.

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

10.2.2.2. 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 (Protocol Attachment 1, Study Schedule).

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

In addition to procedures specified in Protocol Attachment 1, Study Schedule, for children < 6 months old, physical exams and monitoring labs including CBC and comprehensive metabolic testing will be completed after approximately 72 hours of treatment.

In order to address constraints on blood volumes for laboratory tests in younger patients (<1 year), alternative methods of assessing baseline risk of hepatitis, HIV, or TB (e.g. testing of parent) may be considered after discussion with the Sponsor.

10.4. Appropriateness of Measurements

The use of the CANDLE, SAVI, or JDM diary score as a measure of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in autoinflammatory conditions conducted by investigators at the National Institutes of Health. The use of the AGS diary is based on precedent from patients treated by investigators at the Children's National Medical Center, Washington, DC.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Because this study of baricitinib is designed for compassionate use and the conditions being treated are rare, it is anticipated that only a few patients will be enrolled. The data are planned to be summarized with no formal statistical analyses. A formal sample size justification is, therefore, not needed. Eighty five patients are expected to be enrolled.

14. References

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

Attachment 1. Protocol Addendum JAGA(3.3) Original Patient Daily Diary for AGS

AGS Patient Daily Diary

Date of last clinic visit: _____ **Study #:** _____ **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column.

Total Daily Dose _____ **(mg)**

Dose distribution _____ **(mg)**

Dose Frequency - circle or check one. (number of doses per day) If your dose or dose frequency changes, start a new diary page starting with the current day

- **1 time per day** ☐
- **2 times per day** ☐
- **3 times per day** ☐
- **4 times per day** ☐

					0 Able to perform all activities of daily living independently with no restriction.	**0** No crying	**0** sleeps more than 3 hours for infants less than 6 months; more than 6 hours for children over 6 months			**0** No Irritability	**0** No rashes	**0** No rashes	
					5 Able to participate in the following with some level of disability ambulation, communication or fine motor tasks	**1** inconsolable >2 minutes **OR** cry intermittently for <10 minutes"	**1** sleeps 2-3 hours at a time for infants less than 6 months; more than 4-5 hours for children over 6 months			**1** Consoling calms infant in 3-5 minutes	**1** Blotchy red rash which comes and goes	**1** Blotchy red rash which comes and goes	
					7 Requires functional or equipment support for any of the following ambulation, communication or fine mortor tasks	**2** inconsolable >2 minutes **AND** cry intermittently for >10 minutes	**2** sleeps 1-2 hours for infants less than 6 months; more than 2-3 hours for children over 6 months	**0** No seizures	**0** No fever	**2** Consoling calms infant in 6-15 minutes	**2** Persistently red spots which stay	**2** Persistently red spots which stay	
					10 Dependent for all activities of daily living and unable to ambulate, communicate or perform fine motor tasks even with support	**3** Inconsolable for > 10 minutes	**3** sleeps <1 hour for infants less than 6 months; greater than 1-2 hours for children over 6 months	**8** Tonic-clonic, subtle staring, chewing, arching	**1** Temperature greater than or equal to 37.3°C (99.1°F)	**3** Consoling calms in more than 15 min or not at all	**3** Persistent spots which do not blanche when pressed	**3** Persistent spots which do not blanche when pressed	

Day	Date MM/DD/YYYY	Total Daily Dose JAGA (mg) Given	Missed JAGA Dose (mg) & Reason	A.M. Temp	Neurologic Disability	Crying	Length of Uninterrupted Sleep	Generalized Seizure	Fever	Excessive Irritability	Skin Findings on Body	Skin Findings, hands, feet, and ears	Name or initials of person entering information, each day
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
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Site Study Team

Reviewer Name: Reviewer Signature: Date Reviewed:

Attachment 2. Protocol Addendum JAGA(3.3) Example Alternative Patient Daily Diary and Scoring for AGS Patients >6 Months Old

Age		6+ months			
If G tube: poor feeding and regurgitation score maximum					
Medications:					
System	Lilly categories	Signs and Symptoms	Yes/No	Score	Score/JAGA
Central nervous system disturbances	Neurologic disability	Able to perform all activities of daily living or age appropriate milestones independently with no restriction	choose one of these		0
		Able to participate in the following with some level of disability: ambulation, communication or fine motor tasks at an age appropriate level			5
		Requires functional or equipment support for any of the following: ambulation, communication or fine motor tasks at an age appropriate level			7
		Dependent for all activities of daily living and unable to ambulate, communicate or perform fine motor tasks at an age appropriate level even with support			10
	Crying	Cries but easily consolable	choose one of these	0	0
		Excessive or high-pitched cry inconsolable for >2 minutes OR intermittently for >10 min		1	1
		Excessive or high-pitched cry inconsolable for >2 minutes AND intermittently for >10 min		2	2
		Excessive or high-pitched not consolable (cries > 10 mins)		4	3
	Length of uninterrupted sleep	Sleeps >6 hours continuously during night	choose one of these	0	0
		Sleeps 4-5 hour continuously during night		1	1
		Sleeps 2-3 hours continuously during night		2	2
		Sleeps <2 hours continuously during night		3	3
	Excessive irritability	no irritability	choose one of these		0
		consoling calms individual in <6 minutes			1
		consoling calms individual in 6-15 minutes			2
		consoling calms individual in >15 minutes or not at all			3
		No startle reflex	choose one of these	0	
		Mild startle to noise		1	
		Strong startle reflex with noise		2	
		Strong startle reflex with noise including face grimacing, blinking and repeated jerks of arms		3	
		Any startle without noise		4	
		No tremors (shaking, jittering, or shivering movements of the extremities that are not seizures)	choose one of these	0	
		Tremors when disturbed (awoken from sleep, moved, or stimulated)		1	
		Tremors when undisturbed		2	
		No tone issues	choose one of these	0	
		Increased or decreased muscle tone (excessive stiffness or floppiness)		2	
	Generalized seizure	No convulsions or seizures	choose one of these	0	0
		Experienced convulsions or seizures		1	8
Other	Fever	No fever (temperature less than 98.9 F)	choose one of these	0	0
		Low grade fever: 99 - 101 F (37.2-38.3 C)		1	1
		Fever > 101.1 F (>38.4 C)		2	1
		No feeding issues	choose one of these	0	
		Poor feeding (infrequent/uncoordinated suck or dependent on g-tube feeding)		2	
		No regurgitation/vomiting	choose one of these	0	
		Regurgitation/vomiting		2	
	Skin findings body	Skin findings: no skin problem	choose one of these		0
		Skin findings: red patches which fade when pressed with fingers			1
		Skin findings: red patches not fading when pressed with fingers			2
		Skin findings: chronic discoloration			3
	Skin findings hands, face, ears	Skin findings: no skin problem	choose one of these		0
		Skin findings: red patches which fade when pressed with fingers			1
		Skin findings: red patches not fading when pressed with fingers			2
		Skin findings: chronic discoloration			3
		Skin findings: no skin problem in any location	choose one of these	0	
		Skin findings: red patches which fade when pressed with fingers in any location		2	
		Skin findings: red patches not fading when pressed with fingers in any location		4	
		Skin findings: chronic discoloration in any location		6	
	Dosing Information	Total Daily Dose (in mg)	Enter Values		
		Dose Distribution (tablet strength in mg)			
		Dose Frequency (twice a day, three times a day, etc)			
		Total daily dose given (in mg)			
		Doses Missed (in mg) and reason			
	Temp	Temperature (indicate F or C)	Record Temperature		

Attachment 3. Protocol Addendum JAGA(3.3) Example Patient Daily Diary and Scoring for AGS Patients ≤6 Months Old

Age		0-6 months			
If G tube: poor feeding and regurgitation score maximum					
Medications:					
System	Lilly categories	Signs and Symptoms	Yes/No	Score	Score/JAGA
Central nervous system disturbances	Neurologic disability	Able to perform all activities of daily living or age appropriate milestones independently with no restriction	choose one of these		0
		Able to participate in the following with some level of disability: ambulation, communication or fine motor tasks at an age appropriate level			5
		Requires functional or equipment support for any of the following: ambulation, communication or fine motor tasks at an age appropriate level			7
		Dependent for all activities of daily living and unable to ambulate, communicate or perform fine motor tasks at an age appropriate level even with support			10
	Crying	Cries but easily consolable	choose one of these	0	0
		Excessive or high-pitched cry inconsolable for >2 minutes OR intermittently for <10 min		1	1
		Excessive or high-pitched cry inconsolable for >2 minutes AND intermittently for <10 min		2	2
		Excessive or high-pitched not consolable (cries > 10 mins)		4	3
	Length of uninterrupted sleep	Sleeps >3 hours continuously during night	choose one of these	0	0
		Sleeps 2-3 hours continuously during night		1	1
		Sleeps > or =1 but <2 hours continuously during night		2	2
		Sleeps <1 hours continuously during night		3	3
	Excessive irritability	no irritability	choose one of these		0
		consoling calms individual in <6 minutes			1
		consoling calms individual in 6-15 minutes			2
		consoling calms individual in >15 minutes or not at all			3
		No startle reflex	choose one of these	0	
		Mild startle to noise		1	
		Strong startle reflex with noise		2	
		Strong startle reflex with noise including face grimacing, blinking and repeated jerks of arms		3	
		Any startle without noise		4	
		No tremors (shaking, jittering, or shivering movements of the extremities that are not seizures)	choose one of these	0	
		Tremors when disturbed (awoken from sleep, moved, or stimulated)		1	
		Tremors when undisturbed		2	
		No tone issues	choose one of these	0	
		Increased or decreased muscle tone (excessive stiffness or floppiness)		2	
	Generalized seizure	No convulsions or seizures	choose one of these	0	0
		Experienced convulsions or seizures		1	8
Other	Fever	No fever (temperature less than 98.9 F)	choose one of these	0	0
		Low grade fever: 99 - 101 F (37.2-38.3 C)		1	1
		Fever > 101.1 F (>38.4 C)		2	1
		No feeding issues	choose one of these	0	
		Poor feeding (infrequent/uncoordinated suck or dependent on g-tube feeding)		2	
		No regurgitation/vomiting	choose one of these	0	
		Regurgitation/vomiting		2	
	Skin findings body	Skin findings: no skin problem	choose one of these		0
		Skin findings: red patches which fade when pressed with fingers			1
		Skin findings: red patches not fading when pressed with fingers			2
		Skin findings: chronic discoloration			3
	Skin findings hands, face, ears	Skin findings: no skin problem	choose one of these		0
		Skin findings: red patches which fade when pressed with fingers			1
		Skin findings: red patches not fading when pressed with fingers			2
		Skin findings: chronic discoloration			3
		Skin findings: no skin problem in any location	choose one of these	0	
		Skin findings: red patches which fade when pressed with fingers in any location		2	
		Skin findings: red patches not fading when pressed with fingers in any location		4	
		Skin findings: chronic discoloration in any location		6	
	Dosing Information	Total Daily Dose (in mg)	Enter Values		
		Dose Distribution (tablet strength in mg)			
		Dose Frequency (twice a day, three times a day, etc)			
		Total daily dose given (in mg)			
		Doses Missed (in mg) and reason			
	Temp	Temperature (indicate F or C)	Record Temperature		

Attachment 4. Protocol Addendum JAGA(3.3) Amendment Summary

Overview

Protocol Addendum I4V-MC-JAGA (3.2) has been revised. The revised protocol addendum is indicated by revision (3.3) and will be used in place of any preceding version of this protocol addendum.

The overall changes and rationale for the changes made to this protocol addendum are as follows:

- This addendum was revised in order to align with JAGA amendment(u), that allows for additional patient enrollment.

Revised Protocol Addendum

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

Synopsis

Number of Planned Patients/Subjects:
Entered: up to 85~~60~~
Enrolled: up to 85~~60~~
Completed: up to 85~~60~~

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Approver: PPD
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Signature meaning: Approved

1. Compassionate Use Treatment Protocol I4V-MC-JAGA(s): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Baricitinib (LY3009104)

Study I4V-MC-JAGA is an open-label compassionate use treatment program to provide baricitinib to patients with conditions expected to benefit from JAK inhibition: CANDLE, CANDLE-related conditions, SAVI, and severe juvenile dermatomyositis. Patients will receive an initial dose based on their weight class and eGFR that may be escalated to determine a tolerable dose. Patients may be dosed for up to 288 weeks. It is anticipated that up to 60 patients may be treated with baricitinib in an individualized manner. The treatment guidelines contained herein are for compassionate use only. Within these guidelines, open-label baricitinib will only be administered to patients who meet inclusion and exclusion criteria.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly: 14 October 2011.
Approval dates for Amendments (a) through (r) are shown on the following page.
Amendment (s) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 23-Sep-2016 GMT

Amendment (a) Electronically Signed and Approved by Lilly: 20 October 2011.
Amendment (b) Electronically Signed and Approved by Lilly: 15 December 2011.
Amendment (c) Electronically Signed and Approved by Lilly: 17 January 2012.
Amendment (d) Electronically Signed and Approved by Lilly: 21 February 2012.
Amendment (e) Electronically Signed and Approved by Lilly: 24 March 2012.
Amendment (f) Electronically Signed and Approved by Lilly: 08 May 2012.
Amendment (g) Electronically Signed and Approved by Lilly: 24 August 2012.
Amendment (h) Electronically Signed and Approved by Lilly: 08 September 2012.
Amendment (i) Electronically Signed and Approved by Lilly: 05 March 2013.
Amendment (j) Electronically Signed and Approved by Lilly: 03 April 2013.
Amendment (k) Electronically Signed and Approved by Lilly: 21 May 2013.
Amendment (l) Electronically Signed and Approved by Lilly: 06 August 2013.
Amendment (m) Electronically Signed and Approved by Lilly: 10 October 2013.
Amendment (n) Electronically Signed and Approved by Lilly: 05 November 2013
Amendment (o) Electronically Signed and Approved by Lilly: 09 December 2013.
Amendment (p) Electronically Signed and Approved by Lilly: 30 January 2014.
Amendment (q) Electronically Signed and Approved by Lilly: 09 May 2014.
Amendment (r) Electronically Signed and Approved by Lilly: 20 February 2015

2. Synopsis

I4V-MC-JAGA (JAGA) is an open-label compassionate use study. Patients who weigh at least 8.5 kg and who are at least 17.5 months of age are eligible to enter this study (patients who weigh less than 8.5 kg or are younger than 17.5 months may be considered for enrollment after discussion with the Sponsor). Throughout the study, the patient's disease severity will be recorded on a daily diary by the patient or patient's parent or legal guardian. Average diary scores and ongoing active clinical disease will define inadequate response to therapy and will be used to trigger changes in daily doses of baricitinib. Once a patient achieves a low average daily diary score (defined below), the investigator will begin to taper the patient's steroid dose (if the patient is receiving steroids). Patients whose average diary score decreases substantially, but who do not meet the threshold for adequate response/steroid weaning may continue in the study, if the investigator and Sponsor agree that the patient has shown favorable response to treatment with baricitinib, and that it is in the best interest of the patient to continue treatment.

Synopsis: Study I4V-MC-JAGA

Name of Investigational Product: Baricitinib	
Title of Study: Compassionate Use Treatment Protocol I4V-MC-JAGA: Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis	
Number of Planned Patients/Subjects: Entered: up to 60 Enrolled: up to 60 Completed: up to 60	**Phase of Development:** Not Applicable for Compassionate Use
Length of Study: Up to 292 weeks Planned first patient visit: Nov 2011	
Objectives: The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, juvenile dermatomyositis (JDM), or SAVI results in a reduction in the patient's mean daily diary scores as follows: • CANDLE diary: reduction in mean daily score to <0.5 • SAVI diary: reduction in mean daily score to <1.0, exclusive of respiratory/breathing symptom, and a <1.0 increase from baseline in the respiratory/breathing symptom • JDM diary: decrease in mean diary score by 1 point in at least 3 categories	
Study Design: An open-label, compassionate use treatment protocol. Patients will be treated for a maximum of 288 weeks followed by an optional 4 week washout period to monitor safety post treatment	
Diagnosis and Main Criteria for Inclusion and Exclusions: Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder for which there is reason to believe that JAK 1/2 inhibition will be beneficial. One such autoinflammatory disorder is chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. CANDLE syndrome typically presents early in infancy with attacks of fever, panniculitis, arthritis, myositis, lipodystrophy, cytopenias, dyslipidemia, growth retardation, and variable elevation of acute-phase reactants. Other patients eligible to be enrolled into this study include those diagnosed with conditions related to CANDLE syndrome involving immune dysregulation: stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), an autoinflammatory syndrome with interferon (IFN) pathway dysregulation, and juvenile dermatomyositis (JDM).	
Investigational Product, Dosage, and Mode of Administration or Intervention: Baricitinib given orally according to the dosing tables.	
Planned Duration of Treatment: Patients may be treated up to 288 weeks.	
Reference Therapy, Dose, and Mode of Administration or Comparative Intervention: Not applicable	
Criteria for Evaluation: Pharmacokinetics/Pharmacodynamics: Plasma samples will be obtained at specified time points. Concentrations of baricitinib will be determined by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method.	
Statistical Methods: 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, data listings will be the main tool 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.	

3. Table of Contents

Compassionate Use Treatment Protocol I4V-MC-JAGA(s) Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, and Severe Juvenile Dermatomyositis

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4. Abbreviations and Definitions

Term	Definition
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and 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.
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 institutional review boards [IRBs]).
AST	aspartate aminotransferase
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BID	Twice daily (divided dose two times per 24 hours)
CANDLE	chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS	cryopyrin-associated periodic syndromes
cGAMP	cyclic guanosine monophosphate- adenosine monophosphate
clinical research physician (CRP)	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
compassionate use	Compassionate use programs provide investigational products to patients for the treatment of a serious or immediately life-threatening disease or condition when there is no comparable or satisfactory alternative therapy available. They may also be referred to as expanded access programs.
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.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
DEG	differentially expressed gene
ECG	electrocardiogram

Electronic case report form (eCRF)	Sometimes referred to as clinical report form. A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
effectiveness	Effectiveness is the measure of the produced effect of an intervention when carried out in a clinical environment.
eGFR	estimated glomerular filtration rate
end of the study	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.
enrollment	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
HBV	hepatitis B virus
HIV	human immunodeficiency virus
i-proteasome	immunoproteasome complex
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
IFN	interferon
IL	interleukin
institutional review board/ethical review board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
IP-10/CXCL10	interferon inducible protein 10/ C-X-C motif chemokine 10
IVIg	intravenous immune globulin
JAGA	I4V-MC-JAGA
JAK	Janus kinase
JDM	juvenile dermatomyositis
JMP	joint contractures, muscle atrophy, and panniculitis
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.

NOMID	neonatal-onset multisystem inflammatory disease
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PK	pharmacokinetic
PPD	purified protein derivative
Ps	psoriasis
PSMB8	proteasome subunit beta type-8
QD	once daily
QID	four times daily (divided dose four times per 24 hours)
RA	rheumatoid arthritis
requesting physician	A physician who has been granted access to investigational product on a compassionate use (or expanded access) basis as a result of an unsolicited request directed to the study sponsor. The requesting physician is responsible for the conduct of a compassionate use study at a study site. If a study is conducted by a team of individuals at a study site, the requesting physician is the responsible leader of the team. Within this protocol, the requesting physician may also be referred to as principal investigator or investigator.
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. In this study, screening involves diagnostic procedures and/or tests (for example, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
STAT	signal transducers and activators of transcription
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TID	Three times daily (divided dose three times per 24 hours)
TNF	tumor necrosis factor
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal

VAS	visual analog scale
WBC	white blood cell

Compassionate Use Treatment Protocol I4V-MC-JAGA(s) Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

5. Introduction

The purpose of this open-label, compassionate use, treatment protocol is to provide baricitinib to patients with CANDLE*, CANDLE-related conditions, SAVI,* and severe juvenile dermatomyositis (JDM) who are not responsive to biologic therapies and who require treatment with high doses of steroids to control systemic signs and symptoms of their condition (or, in the opinion of the investigator, have failed an adequate course of steroids) and are eligible for treatment under this protocol. Baricitinib is an orally administered inhibitor of Janus kinases 1 and 2 (JAK1 and JAK2).

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 active transcription factors and 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 interferons (IFNs), interleukin (IL)-2, IL-6, IL-12, IL-23, 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 (Ps) (Boy et al. 2009; Kremer et al. 2009).

Baricitinib is being investigated for the treatment of inflammatory diseases, including RA and Ps. 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 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 single 5-mg doses to subjects with end stage renal disease. In patients with RA, baricitinib has also been administered at doses of 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.

* CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
SAVI = stimulator of interferon genes (STING)-associated vasculopathy with onset during infancy

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 infections and infestations system/organ class. 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 et al. 2006; Henderson et al. 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 et al. 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 (i.e. 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 IL-1. 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 (NOMID). Most of these diseases include fever, urticaria-like rash, and arthralgia, and are associated with gain of function mutations in the inflammasome, including, but not limited to, mutations in the NLRP3 gene (McGonagle et al. 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 [Kineret®; Biovitrum]) 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 (Arcalyst®; Regeneron) (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 mutations in the proteasome subunit beta type-8 (PSMB8) gene encoding the beta5i 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 gamma IFN, 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 (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) (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 patients do not respond to DMARDs, IL-1 or IL-6 blocking agents or 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). A review of mortality of all reported patients and those seen at the NIH suggests a mortality of more than 20% before the age of 30 (Kim H et al. in press)

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 described 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. Another patient harbors a *de novo* mutation at position c.442G>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 wildtype. 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 tumor necrosis factor (TNF). The clinical phenotype and the increased IFN response gene expression in the peripheral blood suggest a gain of function resulting 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).

- **CANDLE-Related Conditions.** A group of conditions that have very strong IFN response signature have recently been identified in the gene expression studies from whole blood. These conditions share clinical, pathological, and immunological features, which are different from those typically observed in IL-1-mediated autoinflammatory diseases (including NOMID, deficiency of IL-1 receptor antagonist, hyperimmunoglobulin D with periodic fever syndrome, TNF receptor-associated periodic syndrome, and familial Mediterranean fever) that respond to IL-1 inhibition. Many of the IFN-mediated autoinflammatory diseases do not respond to IL-1 blockade and share a clinical phenotype that may include CNS manifestations (CSF pleocytosis, aseptic meningitis, white matter disease, and basal ganglia calcifications), vasculopathy (arterial hypertension, pulmonary hypertension, vascular calcifications or livedo reticularis), metabolic changes (lipodystrophy, dyslipidemia, insulin resistance, or intra-abdominal fat deposition), musculoskeletal manifestations (myositis, arthralgias or arthritis, and/or panniculitis) and hematological manifestations (i.e cytopenias). In these conditions, histologic features of immature neutrophils in the inflammatory infiltrate are commonly seen on skin biopsy (Canna and Goldbach-Mansky 2015).

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.

Conditions of Immune Dysregulation – Juvenile Dermatomyositis (JDM)

JDM is traditionally viewed as an autoimmune (adaptive immune) disease. Characteristic clinical signs and symptoms include fatigue, fever, symmetrical weakness of the proximal musculature, and characteristic cutaneous changes consisting of heliotrope discoloration of the

eyelids, which may be accompanied by periorbital edema and erythematous papules over the extensor surfaces of joints (Gottron papules). JDM may also be associated with panniculitis-induced lipodystrophy and metabolic abnormalities, such as hyperlipidemia. Support for a diagnosis of JDM is provided by elevated serum levels of muscle enzymes and the histopathological observation of inflammatory myositis on muscle biopsy. Peripheral blood cells show a characteristic pattern of high expression of IFN regulated genes (known as an IFN signature).

JDM is the most common form of idiopathic inflammatory myopathy in children, with an average age of onset of 7 years. The incidence of JDM in the United States is between 2.5 and 4.1 per million children (Batthish and Feldman 2011). Approximately one third of JDM patients have monocyclic disease that undergoes permanent remission after treatment with standard therapeutic regimens, including corticosteroids. The remaining JDM population has polycyclic disease, a subset of which has more severe disease that is difficult to treat with associated poorer outcomes. In this latter difficult-to-treat population, corticosteroids are used in combination with other immunosuppressive therapies, including, but not limited to, cyclosporine, cyclophosphamide, and intravenous immunoglobulins. Biologic agents, such as intravenous immunoglobulins, anti-TNF agents, and rituximab, are being used in the clinic as a treatment for the more severe subset of JDM patients (Martin et al. 2012). However, patients with severe JDM are frequently unresponsive to therapy and are unable to reduce steroid use without loss of disease control.

It is hypothesized that the pathogenesis of JDM could be explained, at least in part, by an innate immune dysregulation, suggesting that, similar to CANDLE, JDM may be, at least in part, an autoinflammatory disorder as well as an autoimmune disease as these patients exhibit activation of both innate and adaptive immunity. Patients with severe JDM and patients with CANDLE syndrome show similarity of clinical phenotype with myositis and panniculitis being a typical feature of both conditions.

Myositis-associated and -specific autoantibodies have been seen in approximately 40% of JDM patients (Khanna and Reed 2010) and vascular injury with endothelial dysfunction, complement activation, and antibody deposition on small vessels is also apparent and associated with disease progression. Consistent with the contribution of both innate and adaptive immunity to the disease process, increases in circulating IL-6 and type 1 IFN-induced chemokines, including IFN inducible protein 10/ C-X-C motif chemokine 10 (IP-10/CXCL10) and monocyte chemoattractant protein-1, have been reported in JDM patients (Bilgic et al. 2009; Greenberg 2010). Furthermore, these circulating biomarkers are correlated with global visual analog scale (VAS) scores (Bilgic et al. 2009). IL-6 and Type 1 IFNs signal through the JAK-STAT pathway, supporting a hypothesis that inhibition of this pathway could provide a viable therapeutic option.

Summary

Patients with CANDLE, CANDLE-related conditions, SAVI, and severe JDM who are not responsive to at least 1 biologic therapy (except as noted in the inclusion/exclusion criteria), and

who require treatment with oral corticosteroids (≥0.15 mg/kg/day of prednisone or its equivalent) to control systemic signs and symptoms of their syndrome (or, in the opinion of the investigator, have failed an adequate course of steroids), will be candidates for baricitinib treatment. 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 CANDLE, CANDLE-related conditions, SAVI, and severe JDM for whom biologics have proven to be ineffective, thereby offering these patients an alternative compassionate use therapeutic option.

In Study I4V-MC-JAGA (JAGA), a within-patient dose-escalation treatment regimen of baricitinib will be utilized. Patients will receive an initial dose based upon weight class and eGFR. Patients may then have their dose escalated to determine a tolerable level. Short-term assessment of the potential beneficial effects of baricitinib treatment will be based on a reduction in the average daily diary score and dose of systemic steroids (if the patient is receiving steroids). If treatment with baricitinib appears to be effective, continued treatment with baricitinib may be provided under the provisions of this protocol.

The study will be conducted in compliance with the protocol, good clinical practice (GCP), and applicable regulatory requirements.

5.1. Concept of Autoinflammation

5.1.1. The Role of IL-1 in Autoinflammatory Diseases

The clinical and basic research unraveling of the CIAS1/NLRP3 inflammasome, a crucial platform to activate IL-1β and controlling its release, has revealed a key inflammatory pathway that is not only constitutively activated in CAPS, but also is 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 2011), and cholesterol crystals in coronary artery disease (Goldbach-Mansky 2009; Duewell 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).

5.2. CANDLE Syndrome and Related Non-IL-1 Dependent Autoinflammatory Diseases

An autoinflammatory disorder has recently been characterized that does not respond to treatment with IL-1, TNF, and only partially to IL-6-blocking agents (Liu et al. 2012). CANDLE syndrome 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. 2010; Torrelo et al. 2010).

In an international collaborative effort, 9 patients with the clinical diagnosis of CANDLE syndrome were studied (Liu et al. 2012). Genetic analyses showed that 7 out of 9 patients harbor genetic mutation in PSMB8 of the immunoproteasome complex (i-proteasome). After the original report of CANDLE syndrome 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 **j**oint contractures, **m**uscle atrophy, and **p**anniculitis (Garg et al. 2010). Patients with JMP were recently demonstrated to carry a mutation PSMB8 (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 JMP had more prominent joint contractures and muscle atrophy than patients described as 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 syndrome (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).

5.3. Functional Data Supporting a Rationale to Block IFN Signaling

As mentioned above, empiric treatment with targeted agents to TNF, IL-1, and IL-6 have been unsuccessful. To characterize the inflammatory pathway and to identify therapeutic targets, the cytokine profile, transcriptome, and signaling pathways in these patients has been assessed. Interestingly, IP-10/CXCL10 serum levels, were on average over 77-fold higher than controls. The 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 NOMID, an IL-1 mediated autoinflammatory syndrome, monocytes from CANDLE patients showed stronger STAT-1 phosphorylation in response to all IFN-γ concentrations from 0.1 to 100 IU used for stimulation.

To probe further for 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 ($p<.05$), 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 IPA, 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 the patients received on the IFN-induced genes, blood samples from multiple visits were obtained in 2 patients, including 1 patient treated at different times with anti-TNF-alpha and anti-IL-6 therapy. Although temporary clinical improvement was seen with anti-TNF-alpha and anti-IL-6 treatment (Liu et al. 2012), the "IFN signature" did not improve. IL-6 blocking therapy normalized IL-6 inducible genes and C-reactive protein 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 and STAT-5 were 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.

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

26S proteasomes are multi-subunit protein complexes critical for degradation of polyubiquitynated proteins within cells. The 20S core complex consists of 2 alpha rings and 2 beta rings, each having 7 different alpha (α) or beta (β) subunits. 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 et al. 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 polyubiquitynated 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 syndrome died of cardiac failure at the age of 47. Histological examination of skeletal muscle on autopsy revealed intramitochondrial paracrystalline inclusions and cytoplasmic and myeloid bodies in muscle cells (Oyanagi et al. 1987). Whether the inclusions seen constitute 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.

5.5. In Vitro Evidence for Using a JAK Inhibitor

JAK kinases are critical signaling molecules mediating IFN signaling on the IFN receptors. To determine the effect of a JAK kinase 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).

6. Objectives

6.1. Primary Objective

The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, or JDM results in reduction in the patient's mean daily diary scores as follows:

- CANDLE diary: reduction in mean daily score to <0.5
- SAVI diary: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and respiratory/breathing symptoms score a <1.0 increase from baseline
- JDM diary: reduction in mean score by 1 point in at least 3 categories.

6.2. Secondary Objectives

The secondary objectives are:

- to determine, in patients receiving steroids at baseline, if administration of baricitinib to patients with CANDLE, CANDLE-related conditions, or SAVI results 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, in patients receiving steroids at baseline, if the administration of baricitinib to patients with severe JDM results in a decrease in the daily dose of corticosteroids (systemic corticosteroids <0.2 mg/kg/day oral prednisone or a decrease of at least 25% of the patient's daily dose at baseline).
- to determine if the administration of baricitinib to patients with severe JDM results in a reduction in the patient's mean diary score to <1.0.

7. Investigational Plan

7.1. Summary of Study Design

JAGA is an open-label compassionate use treatment program for patients who weigh at least 8.5 kg and are at least 17.5 months of age (patients who weigh less than 8.5 kg or are younger than 17.5 months may be considered for enrollment after discussion with the Sponsor). Patients will receive an initial dose based on weight class and eGFR. Then the dose may be escalated to determine a tolerable level. 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 steroids), as appropriate.

Screening, Initial Treatment, and Dose Escalation: Screening is a 2- to 28-day period beginning at Visit 1. After receiving written informed consent from the patient or the patient's parent or a legal guardian (hereafter, "parent" refers to "parent or legal guardian") and written assent from the patient (assent is obtained when appropriate—see Section 13.1, Obtaining Informed Consent), patients will be assigned a patient number and will be considered entered into the study and study procedures may begin. Entry procedures will be performed per the Study Schedule (Attachment 1). Patients must complete at least 2 consecutive weeks of diary entries prior to enrollment and receiving the first dose of baricitinib (refer to the Patient Diary and Diary Score section below). If 2 consecutive weeks of diaries, obtained as part of routine care during the 6 weeks prior to entry, are not available at Visit 1, patients can complete the 2 consecutive weeks of diary entries after study consent is signed (study entry) during the screening period, prior to enrollment. Any physical complaints/symptoms that present prior to initiation of treatment with baricitinib will be collected as preexisting conditions on the electronic case report form (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 a serious adverse event (SAE). Information regarding use of concomitant medications will also be collected on the eCRF.

Baricitinib will be dosed by patient weight range and eGFR. See Table JAGA.7.1 for the dosing schedule for patients with eGFR ≥120 mL/min/1.73 m^2 or Table JAGA.7.2 for patients with eGFR <120 mL/min/1.73 m^2. All patients will receive an initial divided (BID or TID)-daily dose. Patients may have their dose escalated, but must receive a dose for at least 72 hours before a dose escalation can occur. Exceeding the maximum doses shown on the dosing tables is an option, but only with consensus in writing between the investigator and the Sponsor that the dose increase is in the best interest of the patient. Safety laboratory data will be assessed according to the Study Schedule (Attachment 1).

Every effort should be made to follow the dose escalation schedule shown in Table JAGA.7.1. However, if a patient's condition warrants an accelerated dose escalation schedule, this may be allowed after consultation with the Sponsor. 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. Where possible, these decisions should be taken following documented agreement between the investigator and Sponsor; however, in emergency situations the investigator may take these actions. In such situations, the Sponsor should be informed as soon as possible. Any subsequent dose restarts or increments will occur only after review of clinical data and documented agreement between the investigator and Sponsor.

Pharmacokinetic Sampling: Blood samples will be collected to determine baricitinib concentrations. Samples will be collected when the patient reaches steady state at the target dose level after approximately 72 hours of treatment. Alternatively, samples may be collected at the next patient visit. Additional details on PK sampling are provided in Section 10.3.2.

Continuing Treatment: Safety laboratory assessments will be performed and reviewed by the investigator along with a copy of the patient's diary at visits according to the Study Schedule (Attachment 1). AEs and concomitant medications will be assessed. Dosing will follow the regimen shown in Table JAGA.7.1 for patients with eGFR ≥120 mL/min/1.73 m^2, and Table JAGA.7.2 for patients with eGFR <120 mL/min/1.73 m^2. Once the patient has reached a stable dose of baricitinib, the same total dose may be administered as equal or unequal divided doses. For patients with eGFR >120 mL/min/1.73 m^2 and weight <20 kg, the total daily dose can be adminstered up to 4 doses in a day (24 hours). If more than 4 doses are needed in 1 day (24 hours), then consultation and agreement with the Sponsor will be required.

1. If the patient is responding adequately to treatment (average diary score <0.5 or <1.0 [CANDLE or SAVI/JDM diary, respectively]), the patient will continue receiving baricitinib therapy with follow-up appointments according to the Study Schedule (Attachment 1). Steroid weaning may begin for patients who are receiving steroids. If the patient is responding to treatment, but has not met the threshold to begin steroid weaning and is experiencing new or worsening clinically significant adverse effects from steroids (including, but not limited to, cataracts, vertebral fractures due to osteoporosis, Cushinhgoid 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.
2. If a patient continues to have an inadequate response to the baricitinib dose as evidenced by an elevated diary score (average diary score >0.5 or >1.0 [CANDLE or SAVI/JDM diary, respectively]) or ongoing clinical disease activity reflected by increased symptoms or elevated markers of inflammation, the dose should be increased in the dose escalation steps shown in Table JAGA.7.1 or Table JAGA.7.2. The reason for dose increase will be documented in the medical record. Patients must have received a dose for at least 72 hours before continuing to the next dose increase. Every effort should be made to follow the dose escalation schedule shown in Table JAGA.7.1. However, if a patient's condition warrants an accelerated dose escalation schedule, this may be allowed after consultation with the Sponsor.

3. If a patient reaches the maximum allowable dose as specified in (Table JAGA.7.1 or Table JAGA.7.2) and has an inadequate response to treatment, the patient may be discontinued from the study to pursue other treatment options, or one or both of the following may be considered after consultation with the Sponsor:

    (1) Once the patient has reached a stable dose of baricitinib, the same total daily dose may be administered at greater frequency as equal or unequal divided doses (up to 4 doses in 1 day [24 hours]).

    (2) The patient's dose may be increased above the maximum dose shown in Table JAGA.7.1 or Table JAGA.7.2 if, in the opinion of the investigator, this dose increase is warranted based on the clinical assessment of the patient, evaluation of available PK data, and evaluation of renal function. The Sponsor must be consulted before the dose is increased in excess of the maximum dose shown in the dosing tables. For each affected study patient, the conclusion of this consultation must be documented in a way that confirms consensus between the investigator and the Sponsor.

4. If a patient continues to have an inadequate response to treatment after considering the dose modification options identified in item 3 above, then the patient will be discontinued from baricitinib. The patient will return for a follow-up safety visit approximately 28 days after their last dose of investigational product and will discontinue from the study.

5. If a patient reaches the maximum allowable dose (or had a dose modification as described in item 3 above) and his or her average diary score has decreased, but has not met the threshold for adequate response/steroid weaning (does not reach an average diary score of <0.5 or <1.0 [CANDLE or SAVI/JDM diary, respectively]), the patient may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment.

Follow-up appointments will continue during the treatment period according to the Study Schedule (Attachment 1). Each patient's concomitant medications, investigational product compliance, height, weight, vital signs, and AEs will be assessed; and routine chemistry, hematology, and urinalysis assessments will be performed according to the Study Schedule (Attachment 1). A physical exam will be conducted according to the Study Schedule (Attachment 1).

As the conditions being treated in this compassionate use program are rare, patients may be enrolled who must travel a considerable distance to the investigative site. For most of the required visits patients should be seen in-person at the investigative site. Once patients achieve a stable dose, some required visits may be performed as a telephone visit. If a telephone visit is performed, laboratory samples should be obtained locally. Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. An optional 4-week washout period (Visit 801) is included to allow monitoring of patient safety after discontinuing baricitinib treatment in JAGA.

Baricitinib will be provided to an individual patient for up to 288 weeks. As additional safety information is obtained from ongoing clinical trials for baricitinib, additional access to baricitinib for a longer period of time will be considered. After the trial period under this study, the Sponsor will assess the benefit/risk balance for continued access to baricitinib. If no new safety concerns are detected, this study may be amended to allow for continued dosing of baricitinib for another set period of time. Figure JAGA.7.1 illustrates the study design.

Table JAGA.7.1. Dose Escalation Schedule for Patients with eGFR ≥120 mL/min/1.73 m^2

Initial Dose

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	≥120	2 mg	2 mg	2 mg	6 mg	72 hours	0.3/NA	TID
20-40 kg	≥120	3 mg	—	3 mg	6 mg	72 hours	0.15/0.3	BID
>40 kg	≥120	4 mg	—	4 mg	8 mg	72 hours	NA/0.2	BID

First Dose Escalation

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	≥120	2 mg	2 mg 2 mg	2 mg	8 mg	72 hours	0.4/ NA	QID
20-40 kg	≥120	3 mg	2 mg	3 mg	8 mg	72 hours	0.2/0.4	TID
>40 kg	≥120	5 mg	—	5 mg	10 mg	72 hours	NA/ 0.25	BID

Second Dose Escalation (only in patients > 40 kg)

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
>40 kg	≥120	6 mg	—	6 mg	12 mg	72 hours	NA/0.3	BID

Abbreviations: max = maximum; min = minimum; NA = not applicable.

— indicates no further dose escalation allowed.

a See Section 9.4 if a change in the patient's weight during the study would place the patient in a different weight range.

b After reaching a stable dose, the total daily dose can be administered as equal or unequal divided doses.

c Duration of treatment prior to escalation includes days to obtain samples and results from safety blood test assessments prior to the first dose or first dose increase.

d Dose in mg/kg for the lowest weight and highest weight in each weight class.

Table JAGA.7.2. Dose Escalation Schedule for Patients with eGFR <120 mL/min/1.73 m^2

Initial Dose[a]

Weight Class[b]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	<120	2 mg	—	2 mg	4 mg	72 hours	0.2/NA	BID
20-40 kg	<120	2 mg	—	2mg	4 mg	72 hours	0.1/0.2	BID
>40 kg	<120	2 mg	—	2 mg	4 mg	72 hours	NA/0.1	BID

First Dose Escalation (only for patients with eGFR ≥ 60 mL/min/1.73 m^2)

Weight Class[b]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	60-119	2 mg	2 mg	2 mg	6 mg	72 hours	0.3/NA	TID
20-40 kg	60-119	3 mg	—	3 mg	6 mg	72 hours	0.15/0.3	BID
>40 kg	60-119	3 mg	—	3 mg	6 mg	72 hours	NA/0.15	BID

a Baricitinib should not be used in patients with eGFR < 30 mL/min/1.73 m^2.

b See Section 9.4 if a change in the patient's weight during the study would place the patient in a different weight range.

c Duration of treatment prior to escalation includes days to obtain samples and results from safety blood test assessments prior to the first dose or first dose increase.

d Dose in mg/kg for the lowest weight and highest weight in each weight class.

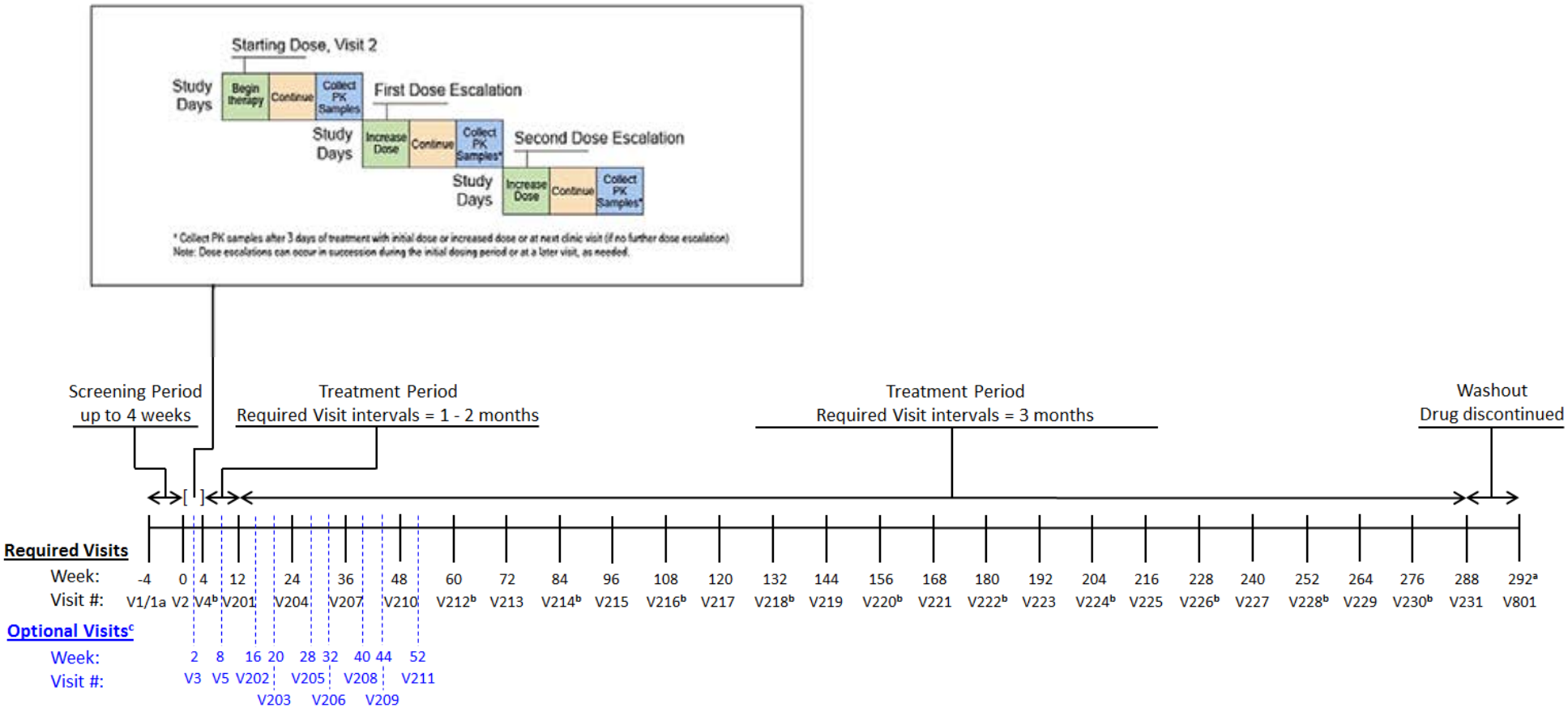

Figure JAGA.7.1. Protocol I4V-MC-JAGA study design.

Abbreviations: PK = pharmacokinetics; V = visit.

a V801 (optional) should occur approximately 28 days after the last dose of investigational product.

b These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, laboratory samples should be obtained and tested locally, and a copy of the laboratory report sent to the PI.

c Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained and tested locally, and a copy of the laboratory report sent to the PI.

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 (that is, CANDLE, JDM, or SAVI). The patient diaries are shown in Attachment 4. 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. During clinic visits, it is preferable that the patient or caregiver complete the patient diary rather than site staff.

The patient or caregiver will be instructed to rate each symptom (fever, rash, musculoskeletal pain, and fatigue [all diaries], headache [CANDLE and JDM diaries], weakness [JDM 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]). 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.

The diary is to be completed daily throughout the study. The diary score is used to assess disease activity and inform the need for an additional dose increase (up to the maximum allowed dose as detailed in Table JAGA.7.1) or initiation of steroid weaning as described (if the patient is receiving steroids). At each visit, the investigator will calculate the average score for each symptom being collected on the diary (that is, the average of the daily scores since the previous visit, correcting for any day for which diary scores were not recorded). The investigator 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. An average diary score ≥0.5 (CANDLE diary) or ≥1.0 (JDM or SAVI diary) or ongoing clinical disease activity reflected by increased symptoms not captured on the diary will be indicative of a lack of complete response and will trigger a dose escalation. An average diary score <0.5 (CANDLE diary) or <1.0 (JDM or SAVI diary) will be indicative of a response to treatment and may trigger initiation of steroid weaning (if the patient is receiving steroids). Additionally, if the patient is responding to treatment, but has not met the average diary score threshold to begin steroid weaning and is experiencing new or worsening clinically significant adverse effects from steroids (including, but not limited to, cataracts, vertebral fractures due to osteoporosis, Cushinhgoid 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. The investigator should review the entire diary and average diary scores at each visit. If there is a trend in the diary scores, (that is, 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.

Patients whose average diary scores decrease after receiving the maximum allowable dose level of baricitinib (as defined in Table JAGA.7.1 or Table JAGA.7.2), but do not meet the threshold for steroid weaning (for patients receiving steroids at baseline), or an adequate response (do not reach an average daily CANDLE diary score <0.5 or a JDM or SAVI diary score <1.0), may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment. This will not be considered to be a protocol violation.

7.2. Discussion of Design and Control

This compassionate use study is an open-label, single-arm design intended to provide baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, or severe JDM. Baricitinib has not been investigated in children; therefore, patients will receive an initial dose that may be escalated using dose escalation tables to an effective and tolerable dose. The dose-escalation period allows for safety assessments in between dose escalations. This study, by the nature of compassionate use, is not intended to answer any research hypothesis; however, it is intended to provide a potential treatment for inflammatory conditions proven resistant to other therapies. Though the open-label, single-arm design has potential for the introduction of bias, the study design represents an ethical approach for treatment of these conditions within a compassionate use framework. An optional 4-week washout period (Visit 801) is included to allow monitoring of patient safety after discontinuing baricitinib treatment in JAGA.

Continued ongoing inflammation at the organ level causes organ damage and results in significant morbidity and mortality. 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 and unsustainable chronic doses of steroids, a compassionate use study is appropriate.

8. Study Population

Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder such as CANDLE syndrome, CANDLE-related syndrome, or SAVI or will have been diagnosed with severe JDM.

Patients who meet all of the inclusion criteria (Section 8.1) and do not meet any of the exclusion criteria (Section 8.2) may enter the study (that is, sign consent). In addition, patients must meet the enrollment criteria (Section 8.3) in order to be eligible to receive baricitinib. Given the severity of these diseases and the absence of other therapeutic options, any patient that does not meet inclusion, exclusion, and/or enrollment criteria may still be considered for enrollment upon consultation with the Sponsor and assessment of the benefits and risks.

8.1. Inclusion Criteria

Patients are eligible for entry into the study (that is, eligible to sign consent) only if they meet **all** of the following criteria:

1) Have systemic signs and symptoms of inflammation as manifested by the presence of 2 or more of the following symptoms: rash, fever, musculoskeletal pain, headache, fatigue, weakness, respiratory/breathing symptoms, or ulcers/ischemic lesions.

2) Have an average daily diary score of ≥0.5 (CANDLE diary) or ≥1.0 (SAVI or JDM diary) assessed over at least 2 consecutive weeks during the 6 weeks prior to entry, if available. Otherwise, patients can complete the diary after study consent is signed during the screening period and meet the inclusion criteria for enrollment into the study.

3) Are ≥17.5 months of age. Patients younger than 17.5 months of age can be considered for enrollment after discussion with the Sponsor.

4) Are ≥8.5 kg in body weight. Patients weighing less than 8.5 kg can be considered for enrollment after discussion with the Sponsor.

5) Have been previously treated with at least 1 biologic therapy and, in the opinion of the investigator, did not respond or are no longer responding to therapy. If the patient has been diagnosed with CANDLE or an equivalent syndrome with decreased proteasome function, or SAVI, the need for previous biologic therapy is not required.

6) Require treatment with oral corticosteroids (≥0.15 mg/kg/d of prednisone or its equivalent) for control of systemic signs and symptoms of their chronic inflammatory disease for at least 2 weeks prior to study entry, or in the opinion of the investigator, have failed an adequate course of steroids.

7) Have had previous documented elevations in acute-phase reactants (for example, high sensitivity C-reactive protein) considered to be the result of the inflammatory disease (patients with CANDLE or CANDLE-related conditions only).

8) Have the ability to provide informed consent or have a legal representative who is willing and able to provide written informed consent, provided that assent is obtained from patients at an age-appropriate level.

8.1.1. Patients with Juvenile Dermatomyositis

Patients with JDM are eligible for entry into the study (that is, eligible to sign consent) only if they meet **all** of the previous criteria (1 through 8) and all of the following criteria:

37) Meet definite or probable JDM diagnosis by the criteria of Bohan and Peter (1975) (Attachment 6) with onset of first symptom prior to 18 years of age.

38) Have refractory myositis as defined by the intolerance to, or an inadequate response to, corticosteroids plus an adequate regimen of at least 2 other immunomodulatory or immunosuppressive agents (including at least 1 biologic agent), such as intravenous immune globulin (IVIg), azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, tacrolimus, or cyclosporine A. Other immunomodulatory or immunosuppressive agents, such as rituximab, can be considered after discussion with the Sponsor. The definition of intolerance is side effects that require discontinuation of the medication or an underlying condition that precludes the further use of the medication.

- Adequate treatment with corticosteroids or immunosuppressive/ immunomodulatory drugs is defined as the lowest of the following doses:
    - Corticosteroids: 1.0 mg/kg/d or 60 mg/d for at least 1 month
    - Azathioprine: 2 mg/kg/d or 150 mg/d for at least 3 months
    - Methotrexate: 0.3 mg/kg or 15 mg/m^2/week or 15 mg/week for at least 3 months
    - IVIg: 1 g/kg/month or 60 g/month for at least 3 months
    - Mycophenolate mofetil: 30 mg/kg/d or 1000 mg twice daily for at least 3 months
    - Cyclophosphamide: 1.0 mg/kg/d or 500 mg/m^2/month or 500 mg/month intravenously for at least 3 months
    - Tacrolimus: 0.1 mg/kg/d or 5 mg/d for at least 3 months
    - Cyclosporine: 2.5 mg/kg/d for at least 3 months

39) If receiving hydroxychloroquine, must have been receiving a stable dose for at least 4 weeks prior to screening visit

40) If receiving a statin, must have been receiving a stable dose for at least 8 weeks prior to screening visit.

8.1.2. Patients with CANDLE-Related Conditions

Patients with CANDLE-related conditions are eligible for entry into the study (that is, eligible to sign consent) only if they meet all of the common inclusion criteria (1 through 8) and all of the following criteria:

46) Have organ specific inflammation involving at least one of the following: vasculopathy (such as arterial hypertension, pulmonary hypertension, vascular calcifications such as basal ganglia calcifications, or livedo reticularis), metabolic changes (such as lipodystrophy, dyslipidemia, insulin resistance, or intra-abdominal fat deposition), musculoskeletal manifestations (myositis, arthralgias or arthritis, and/or panniculitis), hematological manifestations (i.e cytopenias) and/or interstitial lung disease.

47) Have a history of high IP-10/CXCL10 levels and/or IFN response signature in peripheral blood mononuclear cells being one of the most dysregulated blood signatures.

8.2. Exclusion Criteria

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

9) Have received an immunosuppressive biologic agent/monoclonal antibody within 4 half-lives prior to entry, for example, anakinra (4 half-lives=18 hours); etanercept (4 half-lives=18 days); infliximab; or adalimumab (4 half-lives=36 days). Use of IVIg is permitted. Exceptions may be considered after discussion with the Sponsor.

10) Are pregnant or nursing at the time of entry

11) Are females of childbearing potential who do not agree to use 2 forms of highly effective 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 investigational product

    Females of nonchildbearing potential are defined as women ≥60 years of age, women ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, or women who are congenitally or surgically sterile (that is, have had a hysterectomy or bilateral oophorectomy or tubal ligation).

    The following birth control methods are considered highly effective (the patient should choose 2 to be used with their male partner):

    - oral, injectable, or implanted hormonal contraceptives
    - condom with a spermicidal foam, gel, film, cream, or suppository
    - occlusive cap (diaphragm or cervical/vault caps) with a spermicidal foam, gel, film, cream, or suppository
    - intrauterine device
    - intrauterine system (for example, progestin-releasing coil)

- vasectomized male (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate)

  Note: when local guidelines concerning highly effective methods of birth control differ from the above, the local guidelines must be followed.

12) Are males who do not agree to use 2 forms of highly effective birth control (see above) 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 investigational product.

13) Have had symptomatic herpes zoster infection within 12 weeks prior to entry or during the screening period

14) Have a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster, central nervous system involvement, postherpetic neuralgia)

15) Have evidence of active infection, at the time of entry or during the screening period, that, in the opinion of the investigator, would pose an unacceptable risk for participating in the study.

16) Have a history of active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).

17) Have documented high titer autoantibodies suggestive clinically of autoimmune diseases other than severe JDM.

18) Are immunocompromised and, in the opinion of the investigator, are at an unacceptable risk for participating in the study.

19) Have had a serious systemic or local infection (including an infectious mononucleosis-like illness or herpes zoster) within 12 weeks prior to entry or during the screening period. Exceptions include SAVI patients with infected ulcerative skin lesions, which in the opinion of the investigator, would not pose an unacceptable risk for pariticipating in the study.

20) Have been exposed to a live vaccine within 12 weeks prior to entry or are expected to need/receive a live vaccine (including herpes zoster vaccination) during the course of the study

    Note: Investigators should review the vaccination status of their patients and follow the local guidelines for vaccination with nonlive vaccines intended to prevent infectious disease prior to entering patients into the study.

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

22) 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.

23) Have an estimated glomerular filtration rate (eGFR) based on the most recent available serum creatinine of <40 mL/min/1.73 m^2.

24) Have or have had a history of lymphoproliferative disease; or 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.

25) Have a history of chronic alcohol abuse or intravenous drug abuse within the 2 years prior to entry.

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

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

28) Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or non-approved use of a drug or device (other than the investigational product used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

8.2.1. Patients with Juvenile Dermatomyositis

Patients with JDM will be excluded from the study if they meet **any** of the previous criteria (9 through 28) or any of the following criteria:

41) Have drug-induced myositis (myositis in patients taking medications known to induce myositis-like syndromes, including, but not limited to, statin agents, fibric acid derivatives, colchicine, and hydroxychloroquine).

42) Have a history of juvenile polymyositis, inclusion body myositis, or cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer except basal or squamous cell skin cancer or carcinoma in situ of the cervix if at least 5 years since excision.

43) Have myositis in overlap with another connective tissue disease (CTD) that precludes the accurate assessment of a treatment response (for example, difficulty in assessing muscle strength in a scleroderma patient with associated myositis).

44) Have joint disease or other musculoskeletal condition, which precludes the ability to quantitate muscle strength.

8.3. Enrollment Criteria

8.3.1. Inclusion Criteria for Study Enrollment

Entered patients are eligible for enrollment into the study (that is, eligible to receive baricitinib) only if they continue to meet **all** of the common inclusion criteria and applicable disease-specific inclusion criteria for entry (Section 8.1) at the time of Visit 2 plus the following requirement(s):

29) Have a mean daily diary score of ≥0.5 (CANDLE diary) or ≥1.0 (SAVI or JDM diary) assessed over at least 2 consecutive weeks during the 6 weeks prior to entry or after entry but prior to enrollment for patients who completed the diary after consent was signed.

45) For JDM patients, have severe disease as assessed by core set measures (Attachment 6). Severe disease will be assessed as follows: baseline manual muscle testing (within the previous month), with a score no greater than 125 of a possible 150 in conjunction with 2 of the following abnormal core set measures:

- Parent/patient global VAS with a minimum value of 2.0 cm on a 10 cm scale (Attachment 7).
- Physician global VAS with a minimum value of 2.0 cm on a 10-cm scale (Attachment 8).
- Childhood Health Assessment Questionnaire or Health Assessment Questionnaire disability index of ≥0.25.
- Elevation of at least one of the muscle enzymes (creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase [ALT], and aspartate aminotransferase [AST]) at a minimum level of 1.3 × the upper limit of normal (ULN).
- Global extramuscular disease activity score with a minimum value of 1.0 cm on a 10-cm VAS scale (this measure is the physician's composite evaluation and is based on assessments of activity scores on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac scales of the Myositis Disease Activity Assessment Tool (Attachment 9).

8.3.2. Exclusion from Study Enrollment

Entered patients are ineligible for enrollment (that is, ineligible to receive baricitinib) and should be discontinued from the study if they meet any of the following criteria:

30) Have screening laboratory test values outside the reference range for the population or investigative site that, in the opinion of the investigator, pose an unacceptable risk for the patient's participation in the study.

31) Have any of the following specific abnormalities on screening laboratory tests:

- AST or ALT >2 × ULN unless the hepatitis is confirmed as resulting from the autoinflammatory condition. If autoinflammatory-associated hepatitis is present, AST or ALT cannot exceed 4 × ULN. If inflammatory myositis is present or suspected, obtain total and direct bilirubin, aldolase, and gamma-glutamyl transferase if not yet done. Elevation in AST and/or ALT is acceptable if gamma-glutamyl transferase and total and direct bilirubin are less than 1.5 × ULN and an expert independent of the principal investigator (preferably a hepatologist or gastroenterologist) documents that the elevation is secondary to myositis. Even if inflammatory myositis is considered present, AST or ALT cannot exceed 5 × ULN.
- Hemoglobin <10 g/dL (100 g/L). Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with hemoglobin <10 g/dL if the anemia is considered a result of the underlying disease (see below).
- Total WBC count <2500 cells/μL. Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with WBC count <2500 cells/μL if the low WBC count is considered a result of the underlying disease (see below).
- Neutropenia (absolute neutrophil count [ANC] <1200 cells/μL). Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with an ANC <1200 cells/μL if the low ANC is considered a result of the underlying disease (see below).
- Thrombocytopenia (platelets <100,000/μL). Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with a platelet count <100,000/μL if the low platelet count is considered a result of the underlying disease (see below).
- eGFR <40 mL/min/1.73 m^2

Note: A patient with CANDLE, CANDLE-related condition, or SAVI may be enrolled with any of the above specific abnormalities on screening laboratory tests if these laboratory abnormalities are considered a feature of the disease. An expert independent of the principal investigator (preferably a hematologist) must evaluate the patient and, in conjunction with the principal investigator, document that the laboratory abnormality is a feature of the underlying CANDLE, CANDLE-related condition, or SAVI condition; the investigator must also consult with the Sponsor before the patient can be enrolled.

32) Have screening thyroid-stimulating hormone and/or thyroxine values outside of the laboratory's reference range and are assessed to be clinically significant. If results are available from testing within 1 month, 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, laboratory tests may be repeated once within 1 week of the initial values, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

33) 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 (for example, Bazett's corrected QT interval >450 msec for males and >470 msec for females).

34) Have evidence of active or latent TB as documented by a positive purified protein derivative (PPD) test (≥5 mm induration between approximately 2 and 3 days after application, regardless of vaccination history), medical history, and chest x-ray at screening. If results are available from testing within 1 month, then the patient will not have to be retested. Exceptions include patients with a history of latent TB who have documented evidence of completing a course of appropriate treatment:

- If the PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active or latent TB, the patient should have a QuantiFERON®-TB Gold test. If the test is positive or indeterminate, the patient is excluded from the study.
- The QuantiFERON®-TB Gold test may be used instead of the PPD test; patients with positive tests are excluded. If the QuantiFERON-TB Gold test is indeterminate, a retest is allowed. If the retest is also indeterminate, the patient is excluded from the study.

35) Have a positive test for hepatitis B defined as (1) positive for hepatitis B surface antigen, or (2) positive for anti-hepatitis B core antibody, but negative for hepatitis B surface antibody unless the anti-hepatitis B core antibody is thought to be a false positive result. In the latter case, confirmation of the presence of hepatitis B virus (HBV) by DNA testing is required. An HBV DNA indeterminate result is considered HBV infection.

    If results are available from testing within the previous 3 months, then the patient will not have to be retested:

- If any of the hepatitis B tests have an indeterminate result, confirmatory testing will be performed by an alternate method.

36) Have hepatitis C virus (positive for anti-hepatitis C antibody with confirmed presence of hepatitis C virus); have evidence of HIV infection, and/or positive HIV antibodies. If results are available from testing within the previous 3 months, then the patient will not have to be retested.

Patients who are entered, but do not meet enrollment criteria, should be discontinued from the study. These patients can be re-entered into the trial (that is, be reconsented) if the investigator believes that the patient might meet enrollment criteria at a future date, taking into consideration the volume of blood required for rescreening.

8.4. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [9] excludes individuals taking medications that may confound or may interfere with the ability to assess the safety and efficacy of baricitinib. Exclusion Criteria [10] to [12] exclude individuals who are pregnant, breastfeeding, at risk for becoming pregnant, or at risk for impregnating their partner during the study. Exclusion Criteria [13] to [21] and [34] to [36] exclude individuals who are at an increased risk for infections or infectious complications. Exclusion Criteria [22] to [25] and [30] to [33] exclude individuals with concomitant medical conditions that increase the risk for their participation in the study. Exclusion Criteria [26] to [28] exclude individuals who may not be compliant with study-related procedures or whose participation in the study may introduce bias. Exclusion Criteria [41] through [44] exclude JDM patients who may have another myositis condition that would preclude accurate muscle strength assessment.

8.5. Discontinuations

8.5.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be discontinued from the investigational product, but may be allowed to continue in the study in order to provide follow-up data. An exception may be granted in rare circumstances where the patient has a serious or life-threatening condition for which there is no effective alternative therapy and, in the opinion of the investigator, is receiving benefit from investigational product. In these rare cases, the investigator must obtain documented approval from Eli Lilly and Company (Lilly) to allow the patient to continue to receive investigational product.

8.5.2. Interruption of Investigational Product

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 the Sponsor must be contacted to discuss and document the appropriate course of action which may include a nephrology evaluation.

As listed in Table JAGA.8.1, certain situations necessitate a discussion with the Sponsor 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 JAGA.8.1 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 JAGA.8.1. Guidance on Interruption of Investigational Product

Hold investigational product if the following laboratory test results occur, unless continuation of investigational product is approved by the Sponsor with documentation:	If investigational product was stopped, it may be restarted after discussion with the Sponsor or when:	Additional instructions:
WBC count <2,000 cells/µL[a]	WBC count ≥2,000 cells/µL	None
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.)	None
Lymphocyte count <500 cells/µL[a]	Lymphocyte count ≥500 cells/µL	None
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.)	None
eGFR <40 mL/min/1.73 m^2 (from serum creatinine)[b]	eGFR ≥40 mL/min/1.73 m^2	Repeat BK titers in blood and urine. Nephrology evaluation may be indicated
ALT or AST >5 x ULN or ALT or AST >3 x ULN and total bilirubin >2 x ULN	ALT and AST return to <2 x ULN, and investigational product is not considered to be the cause of enzyme elevation.	See Recommended Hepatic Evaluation Guidance Document (Attachment 3).
Hemoglobin <8 g/dL[a]	Hemoglobin ≥8 g/dL	None
HBV DNA ≥ lower limit of quantification [c]	At the discretion of the investigator after consultation with the Sponsor.	None
Malignancy	At the discretion of the investigator after consultation with the Sponsor.	None
Pregnancy	At the discretion of the investigator after consultation with the Sponsor.	None

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; ULN = upper limit of normal; 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. An expert independent of the principal investigator (preferably a hematologist) must evaluate the patient and, in conjunction with the principal investigator, determine and document that the laboratory abnormality is related to the underlying disease; the investigator must also consult with the Sponsor 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 the Sponsor, 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 pre-existing renal impairment, a lower threshold for interruption may be considered after discussion with the Sponsor.

[c] If a HBV DNA result of 'target detected'(above the lower limit of quantification), then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study drug 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.

8.5.2.1. Discontinuation from Investigational Product

Any patient who is permanently discontinued from investigational product for an abnormal laboratory result should have the abnormal laboratory result reported as an AE, or an SAE if the laboratory abnormality results in an outcome requiring the AE to be reported as an SAE.

In addition, patients may be discontinued from the investigational product or from the study 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.
  - 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.
    - It is possible that a JAK inhibitor similar to Lilly's baricitinib may become commercially available before baricitinib. Once a JAK inhibitor becomes commercially available, Lilly's compassionate use program for baricitinib may be discontinued. Should another medication with potential to treat this patient population become commercially available before Lilly's baricitinib, the compassionate use program for baricitinib may be discontinued.

- 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.
- Adverse Event
  - The investigator decides that the patient should be withdrawn. If this decision is made because of an SAE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations Section 10.2.

Patients who discontinue the investigational product and/or study early will have end-of-study procedures performed as shown in the Study Schedule (Attachment 1).

8.5.3. Discontinuation of Study Sites

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

8.5.4. 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.

9. Treatment

9.1. Treatments Administered

All eligible patients will receive treatment with baricitinib as a twice-daily dose or multiple divided doses (as described in Section 7.1). Depending upon the prescribed dose and/or the visit number, the dosing will occur during the patient's clinic visit, or packaged baricitinib will be dispensed to the patient to provide enough medication for dosing until the next visit.

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the patient, parent, or legal guardian, verifying that instructions are followed properly, maintaining accurate records of investigational product dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

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

9.2. Materials and Supplies

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

During clinic visits, investigational product may be prepared by a pharmacist or other qualified person using good pharmacy practices. Tablets are not to be split for the purpose of dose adjustment.

Investigational product will be dispensed to the patient at the investigator's study site. As needed, preparation instructions will be provided by the clinical site. Investigational product packaging will be labeled with a unique identifier for drug accountability. Investigational product will be dispensed with additional tablets to allow for sufficient supply.

9.3. Method of Assignment to Treatment

All patients participating in this study will receive open-label baricitinib.

9.4. Rationale for Selection and Timing of Doses in the Study

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 JAGA.7.1 or Table JAGA.7.2 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 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, initial improvements in clinical status were only observed upon achieving a stable 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 autoinflammatory syndromes appears to require higher concentrations of disease-modifying antirhematic 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 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.

Subsequently, based on PK analyses of additional patients in the JAGA program, body weight and renal function (GFR estimated by the Schwartz equation for patients under 18 years and by CKD-EPI for patients older than 18 years) were identified as significant covariates on the apparent volume of distribution (V/F) and apparent clearance (CL/F), respectively, which supports dose adjustments based on weight and eGFR. Among JAGA patients with normal renal function, the observed baricitinib elimination half-life was < 6 hours in nearly all patients. The weight categories and dosing regimens presented in Table JAGA.7.1 and Table JAGA.7.2 are based on observed dose titration and stable dose in the 18 JAGA patients seen at NIH up to 04 March 2016 and the PK analyses from these patients.

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 JAGA.7.1 for patients with eGFR ≥ 120 mL/min/1.73 m^2 and Table JAGA.7.2 for patients with eGFR < 120 mL/min/1.73 m^2. If the patient loses weight during the study, the investigator may opt to keep the patient on their current dose. The investigator should ensure that the increase in weight is not related to fluid retention.

9.5. 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 STAT3-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.

9.6. Continued Access to Investigational Product

Patients may receive baricitinib for up to 288 weeks under the terms of this study.

This study may be terminated at the time of United States commercial availability of baricitinib or at the time of United States commercial availability of a similar JAK inhibitor or another drug

with potential to treat these patients. Baricitinib will no longer be supplied if Lilly stops development of baricitinib for any reason at any time.

9.7. Blinding

This is an open-label study.

9.8. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication eCRF.

9.9. Treatment Compliance

Patient compliance with investigational product will be assessed at each visit. Compliance will be assessed by counting returned tablets. 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.

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Primary Effectiveness Measure

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

10.2. Safety Evaluations

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.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that cause patients to discontinue before completing the study. The patients should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

10.2.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to investigational product or drug-delivery system should be reported. Data on fetal outcome and breast feeding are collected for regulatory reporting and drug-safety evaluation.

Study-site personnel will record the occurrence and nature of each patient's preexisting conditions, including autoinflammatory diseases under treatment in the study.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to study procedures are reported to Lilly or designee.

In addition, all AEs occurring after the patient receives the first dose of investigational product must be reported to Lilly or its designee via eCRFs.

Any clinically significant findings from ECGs, laboratory values, vital-sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to study procedure, studied disease state, investigational product, and/or drug-delivery system via the eCRF.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study-site personnel must clearly report to Lilly or its designee via the eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.2.1.1. Serious Adverse Events

SAE collection begins after the patient has signed informed consent and has received investigational product. If a patient experiences an SAE after signing informed consent, but prior to receiving investigational product, the event will NOT be collected unless the investigator feels the event may have been caused by a study procedure.

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

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. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs occurring after a patient has taken the last dose of investigational product will be collected in the pharmacovigilance system and the clinical data-collection database for 28 days after the last dose of investigational product, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either investigational product, or drug delivery system, or a study procedure.

SAEs that could be expected in the study population independent of drug exposure will be assessed by the Sponsor in aggregate periodically during the course of the trial are not currently defined.

10.2.1.1.1. 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 recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance documents.

10.2.1.2. Adverse Events of Special Interest

Adverse events of special interest include the following:

- infections
- myelosuppressive events of anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia
- thrombocytosis
- elevations in ALT/AST (>3 times ULN) with total bilirubin (>2 times ULN)

Patients with these events will be identified using the same criteria presented in Section 8.5.2 for the interruption of investigational product (Table JAGA.8.1) with the exception of anemia, which will be defined as a hemoglobin <6.5 g/dL, and thrombocytosis, which will be defined as a platelet count >600,000/µL.

10.2.2. Other Safety Measures

10.2.2.1. Electrocardiograms

Twelve-lead ECGs will be obtained according to the Study Schedule (Attachment 1). A single 12-lead ECG measurement will be performed at screening. This screening ECG will be interpreted by a qualified physician (the investigator or qualified designee) at the site to determine whether the patient meets entry criteria.

10.2.2.2. 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 pre-existing 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 (Attachment 1).

10.2.2.3. Vital Signs

Vital signs (eg. blood pressure and pulse) will be measured at times indicated in the Study Schedule (Attachment 1). 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.

10.2.2.4. Chest X-Ray and Tuberculosis Testing

A posterior-anterior view chest x-ray will be obtained, unless results from a chest x-ray obtained within 6 months prior to the study are available and are either normal or show only stable disease. The chest x-ray will be reviewed by the investigator or his/her designee to exclude patients with active TB infection.

In addition, patients will be tested at screening for evidence of active or latent TB indicated by a positive PPD TB skin test response (≥5 mm induration, between approximately 2 and 3 days after test application [visits as indicated on the Study Schedule, Attachment 1], regardless of Bacille Calmette-Guérin vaccination history). If the QuantiFERON-TB Gold test is available and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may be used instead of the PPD TB test (positive tests excluded) and may be read locally. If the QuantiFERON-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

Patients who have a documented history of completing an appropriate TB treatment regimen with no history of re-exposure since their treatment was completed are eligible to participate in the study.

10.2.2.5. Liver-Function Monitoring

Liver-function monitoring will occur frequently throughout the study. If elevations in ALT/AST or total bilirubin occur, the patient should be closely observed as described in Table JAGA.8.1 and the Recommended Hepatic Evaluation Guidance Document (Attachment 3).

10.2.2.6. 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, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide. During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased. See Attachment 1 for frequency of pulmonary function monitoring.

10.2.2.7. 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 Attachment 1.

10.2.3. Safety Monitoring

Lilly will review SAEs within time frames mandated by company procedures. 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 8.5 for discontinuation criteria related to specific AEs.

Vitals signs will be monitored as indicated in the Study Schedule (Attachment 1).

Twelve-lead ECGs will be reviewed for safety. In addition, unscheduled ECGs may be recorded for safety assessments, if clinically indicated.

10.2.4. Complaint Handling

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

Complaints related to unblinded concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.3. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study.

Attachment 1 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study. Fewer invasive sampling may actually occur, but this will not require a protocol amendment.

10.3.1. Samples for Standard Laboratory Testing

Blood and urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, including chemistry, hematology, and urinalysis panels, will be performed. Every effort should be made to obtain all laboratory tests listed in Attachment 2; however, if laboratory tests are not available locally or test results are otherwise missing, this will not be considered a protocol violation. A pregnancy test will be performed (if applicable). Attachment 2 lists the specific tests that will be performed for this study.

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.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.3.2. Samples for Drug Concentration Measurements Pharmacokinetics

Venous blood samples for the measurement of baricitinib concentrations will be collected from all patients enrolled in the study. Samples will be collected after beginning baricitinib therapy and at each dose increase at the time points shown in Table JAGA.10.1. It is also recommended that PK samples be collected more frequently for patients with eGFR < 120 mL/min/1.73 m^2, which may be at every visit if deemed necessary.

Table JAGA.10.1. Pharmacokinetic Sampling

Sampling at Beginning of Treatment and at Each Dose Increase		
Day 1, Start of therapy or day of dose increase	Baricitinib administered at initial dose or baricitinib dose increased (Table JAGA.7.1)	
Day 2	Continue baricitinib	
Day 3 or next clinic visit[a] (if no further dose increase)	Continue baricitinib	Collect 4 PK samples at morning dose: • Pre-morning-dose • 1 hour post-morning-dose • 1.5 hours post-morning-dose • 4 hours post-morning-dose Collect 2 PK samples at evening dose: • Pre-evening-dose • 1.5 hours post-evening-dose

Abbreviations: PK = pharmacokinetic.

[a] If PK samples cannot be processed within the specified time after collection, the PK samples may be collected on the next business day. For all PK samples, the actual date and exact timing (24-hour clock) of PK sample collection and the date, time, and dosage amount of the last 2 doses prior to the PK sample should be recorded.

PK samples must be collected each time the baricitinib dose is increased. If a patient has an adequate response to treatment at a lower dose than the maximum dose, but becomes unresponsive at a later time, the schedule of dose increases and PK sampling can be resumed. If a patient's daily dose is divided into multiple doses, an additional PK sample may be collected pre-dose for each additional dose. For example, a CANDLE patient receiving twice daily dosing who has their total daily dose divided into 3 doses may have a pre-dose PK sample collected before each of the three doses. Additional PK samples may be collected with Sponsor approval to assess safety and dosing.

For all PK samples taken, the actual date and exact timing (24-hour clock) of PK sample collection and the date and time of the last 2 doses prior to the PK sample should be recorded.

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

If the blood volumes required for PK sampling exceed established local guidelines for phlebotomy, then the PK sample collection may be modified.

10.4. Appropriateness of Measurements

The use of the diary score as one of the measurements of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in autoinflammatory conditions conducted by investigators at the National Institutes of Health.

11. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, 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 eCRF data and use standard computer edits to detect errors in data collection

In addition, Lilly or its representatives may 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.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the Sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

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

eCRF data will be encoded and stored in a clinical trial database.

Any data for which paper documentation provided by the patient or parent 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 or parent may include, for example, a paper diary to collect patient-reported outcome measures (for example, a rating scale), a daily dosing schedule, or an event diary.

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Because this study of baricitinib is designed for compassionate use and the conditions being treated are rare, there is no minimum or maximum requirement of the number of patients to be studied.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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, data listings will be the main tool 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.

12.2.2. Patient Disposition

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

12.2.3. Patient Characteristics

A summary and list of demographic information and baseline characteristics of all enrolled patients will be created. Special care will be taken not to include sensitive personal health information that may reveal the identity of the patients.

12.2.4. 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.

12.2.5. Primary Outcome and Methodology

The primary data presentation will be a summary of the percent of patients achieving a decrease in the appropriate diary score. Additional summaries and by-patient listings of the baseline and final steroid doses and displays of changes over time may be created for those patients receiving steroids. No formal statistical test of any hypothesis will be conducted.

12.2.6. Efficacy

A by-patient listing that includes the maximum baricitinib dose received by the patient, the maximum decrease in daily corticosteroid dose for those patients receiving steroids at baseline, and the minimum patient diary score achieved while receiving the maximum baricitinib dose, the reason for discontinuation, and the nature of AEs deemed possibly related to investigational product that were experienced by the patient will be created. Additional data displays and

listings of efficacy measures over time once the patient reaches his/her maximum dose of baricitinib will be created if a sufficient number of patients are enrolled.

12.2.6.1. Pharmacokinetic/Pharmacodynamic Analyses

Population PK analysis will be conducted to characterize PK in patients with CANDLE and SAVI. Pharmacokinetic/pharmacodynamic analyses or other analyses may also be conducted if deemed appropriate.

12.2.7. Safety Analyses

Safety measures will be summarized and/or listed. Standard listings will include TEAEs, SAEs, and results from laboratory tests for each patient. By definition, TEAEs are AEs that begin or increase in severity after the patient receives the first dose of baricitinib. If a sufficient number of patients are enrolled, 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.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient or parent understands the potential risks and benefits of participating in the study, including answering any questions the patient or parent may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient or parent in simple terms before the patient is entered into the study, and to document that the patient or parent is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of investigational product.

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 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 majority 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.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonization guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

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 current Investigator's Brochure or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

(1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines

(2) the International Conference on Harmonization GCP Guideline [E6]

(3) applicable laws and regulations

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

All or some of the obligations of the Sponsor may be assigned to a third-party organization.

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.

13.3.1. Investigator Information

Physicians with a specialty in rheumatology with access to hospitals with appropriate pharmacy support and outpatient management will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

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

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

13.3.3. Final Report Signature

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

The Sponsor's responsible medical officer will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol I4V-MC-JAGA Study Schedule

Study Schedule, Protocol I4V-MC-JAGA

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Informed consent		X										
Demographic characteristics		X										
Height		X		X	X	X	X	X	X	X	X	X
Weight		X		X	X	X	X	X	X	X	X	X
Administer tuberculosis test		X[f]										
Read tuberculosis test			X									
Chest x-ray		X[g]										
Electrocardiogram (ECG)		X										
Review inclusion/exclusion criteria		X										
Medical history		X										
Physical examination		X		X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X	X
Assessment of JDM core measures[h]		X										
Vital signs		X		X	X	X	X	X	X	X	X	X
Diary Scores		X		X[i]	X	X	X	X	X	X	X	X
Concomitant medications		X		X	X	X	X	X	X	X	X	X
Preexisting conditions		X										

*(continued)

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Adverse events				X	X	X	X	X	X	X	X	X
Investigational drug dose modifications				X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]		
Investigational product returned and compliance assessed					X	X	X	X	X	X		
Laboratory												
Hematology		X		X[l]	X	X	X	X	X	X	X	X
Serum chemistry		X		X[l]	X	X	X	X	X	X	X	X
Fasting lipid panel		X					X	X	X	X	X	X
Urinalysis		X		X[l]	X	X	X	X	X	X	X	X
HBsAg, HBcAb, HBsAb		X[m]										
Hepatitis C antibody		X[m]										
HIV		X[m]										
Thyroid stimulating hormone		X[f]										
BK virus quantitative PCR, plasma		X				X		X	X[t]	X[t]	X	X
BK virus quantitative PCR, urine		X				X		X	X[t]	X[t]	X	X

(continued)

Serum pregnancy test[n]	X										
Urine pregnancy test[n]			X	X	X	X	X	X	X	X	X
Plasma baricitinib concentration[o]			X	X	X	X	X	X	X		
Pulmonary function tests (SAVI patients only)[p]	X		X	X	X	X	X	X	X	X	X

Abbreviations: ET = early termination; JDM = juvenile dermatomyositis; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibiody; HBsAb = hepatitis B surface antibody; HIV = human immunodeficiency virus; SAVI = STING-associated vasculopathy with onset during infancy.

a Early termination visit is required if early termination occurs.
b Visits occur at approximately 4-week intervals during Weeks 16 through 52 (including both required and optional visits)
c Visits occur at approximately 12-week intervals during Weeks 60 through 288.
d Visit 2 encompasses the initial dosing period and can vary in time depending on whether the patient progresses through the first and second dose escalation during this period. Four days is the minimum time.
e Every effort should be made to schedule patient visits within the allowable visit window; however, if a patient visit is scheduled outside the visit window, it will not be considered a protocol violation.
f If results are available from testing within 1 month, then the patient will not have to be retested.
g If a chest x-ray has not been performed in the 6 months prior to screening visit.
h Juvenile dermatomyositis patients only.
i At least 2 consecutive weeks of diary scores are required prior to beginning investigational product.
j Each time study dose is adjusted during Visit 2, this eCRF will be completed.
k See dose escalation schedule (**Table JAGA.7.1**). Each time study dose is adjusted, this eCRF will be completed. Samples for chemistry, hematology, and urinalysis may be collected 2 weeks after final dose increase. Collect pharmacokinetic samples as described in Section **10.3.2**.
l Collect prior to each dose escalation. Investigator will review to ensure dose escalation is appropriate.
m If results are available from testing within the previous 3 months, then the patient will not have to be retested.
n 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 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
o Baricitinib concentration samples will be collected as described in Section **10.3.2**. Samples will be collected after Visit 2 if patient has a dose escalation (see **Table JAGA.7.1**) or as needed for safety monitoring in patients with eGFR < 120 mL/min/1.73 m^2.
p Pulmonary function tests are required for SAVI patients only. Pulmonary function tests may include vital signs, pulse oximetry, imaging, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide. During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased.
q These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2.
r Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained locally.
s Optional physical exams may be performed as needed to document clinically active disease, i.e. rash, fever, arthritis, worsening of splenomegaly, hepatomegaly, and corticosteroid side effects i.e. increase in abdominal girth, cataracts, vertebral fractures due to osteoporosis, Cushinhgoid habitus, substantial weight gain, avascular necrosis, dyslipidemia, hypertension, opportunistic infections or stunted growth, hirsutism, acanthosis nigricans and others.t BK virus testing required only at on-site, required visits.

Attachment 2. Protocol I4V-MC-JAGA Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b,c]	**Serum Chemistry**[a,b]
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin[c]
Mean cell volume (MCV)	Direct bilirubin[c]
Mean cell hemoglobin concentration (MCHC)	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT/SGPT)[c]
Reticulocyte	Aspartate aminotransferase (AST/SGOT)[c]
Absolute counts of:	Blood urea nitrogen (BUN)[c]
Neutrophils, segmented	Creatinine[c]
Neutrophils, juvenile (bands)	Calcium
Lymphocytes	Glucose
Monocytes	Albumin
Eosinophils	Total protein
Basophils	Creatine phosphokinase (CPK)
Platelets	Uric acid
	Gamma glutamyl transferase (GGT)
	Aldolase[d]
Lipid[e]	
Total cholesterol (TC)	
Low-density lipoprotein (LDL)	
High-density lipoprotein (HDL)	**Other Tests**[a]
Triglycerides	Hepatitis B Surface antigen (HBsAg)[g]
	Anti-Hepatitis B Core antibody (HBcAb)[g]
Urinalysis[a,b,f]	Hepatitis B Surface antibody (HBsAb)[g]
	Hepatitis B Virus DNA[g]
Specific gravity	Human immunodeficiency virus (HIV)[g]
pH	Hepatitis C antibody[h]
Protein	Thyroid-stimulating hormone (TSH)[g]
Glucose	Thyroxine (T4)[g]
Ketones	Pregnancy Test[i]
Bilirubin	QuantiFERON®-TB Gold[g,j]
Urobilinogen	Baricitinib serum concentration
	BK virus quantitative PCR, plasma
	BK virus quantitative PCR, urine
	Urine cytology
	eGFR
Blood	
Leukocyte esterase	
Nitrite	

Abbreviations: PPD = purified protein derivative; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis; WBC = white blood cells.

Footnotes on next page.

a Assayed by local clinical laboratory.
b Unscheduled blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator.
c If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2.
d Perform if inflammatory myositis is present.
e Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to test.
f Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.
g Test required at Visit 1 only to determine eligibility of patient for the study.
h A positive hepatitis C antibody result will be confirmed with a positive hepatitis C virus result.
i For all women of childbearing potential, a serum pregnancy test will be performed at Visit 1 and a urine pregnancy test (local laboratory) will be performed at Visit 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
j The QuantiFERON®-TB Gold 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. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

Attachment 3. Protocol I4V-MC-JAGA Recommended Hepatic Evaluation Guidance Document

Clinical laboratory investigation is highly recommended for diagnosis and monitoring based on the following recommendations adapted from the Drug Induced Liver Injury Guidance published by the FDA in July 2009. Investigators are encouraged to use clinical judgment and may consult with the Lilly clinical research physician for further clarification as necessary.

If an isolated elevation in ALT/AST ≥3 times and ≤5 times ULN or total bilirubin ≥2 times ULN occurs, the patient should be closely observed, including:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the investigational product has been discontinued and the patient is asymptomatic. Monitor AST, ALT, total bilirubin, and alkaline phosphatase until aminotransferase enzymes (ALT, AST) return to <3 times ULN and total bilirubin level <2 times ULN.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases, including history of liver abnormalities or disease (for example, Gilbert's disease) in the patient's family
- Obtaining a history of recent concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtaining a history of exposure to environmental chemical agents (for example, occupational or recreational exposure)
- Obtaining additional tests to evaluate liver function, as appropriate (for example, international normalized ratio, direct bilirubin)
- Consider obtaining gastroenterology or hepatology consultations

In patients with JDM, elevations in ALT/AST up to 5 times ULN may be determined to be myositis-related, subject to the results of additional investigations and clearly stated independent expert opinion, as described in exclusion criterion 31, Section 8.3.2.

If an isolated elevation in ALT/AST >5 times ULN, perform all of the above and obtain gastroenterology or hepatology consultation.

Attachment 4. Protocol I4V-MC-JAGA Patient Diaries

CANDLE and CANDLE - Related Diary

Date of last clinic visit: _____ **Study #:** _____ **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column.

Total Daily Dose _____ **(mg)**

Dose breakdown _____ **(mg)**

Dose Frequency - circle or check one. (number of doses per day)
If your dose or dose frequency changes, start a new diary page starting with the current calendar day.

- 1 time per day ☐
- 2 times per day ☐
- 3 times per day ☐
- 4 times per day ☐
- 5 times per day ☐

0 = No fever	**0** = No rash	**0** = No pain	**0** = No headache	**0** = No fatigue
1 = Fever without impact on daily activity	**1** = Rash barely present	**1** = Mild pain not requiring medication, no limping	**1** = Mild headache not requiring medication or any adjustments of daily activities	**1** = Mild fatigue, no functional impact
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	**2** = Rash covering 10% of body surface area	**2** = Pain requiring medication or leading to limping or other mild functional impact	**2** = Headache requiring medication or having mild functional impact	**2** = Moderate fatigue with mild functional impact
3 = Fever requiring medication with significant impact on daily activities (missing school, listlessness)	**3** = Rash covering more than 30% of body surface area	**3** = Pain requiring medication or having a severe functional impact	**3** = Headache requiring medication and having a severe functional impact	**3** = Severe fatigue with a severe functional impact
4 = Fever forcing the patient to be bedridden	**4** = Worst rash ever or covering over 30% of body surface area or hurting or stinging	**4** = Severe pain, child refusing to walk, or staying in bed most of the time	**4** = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	**4** = Severe fatigue resulting in patient staying in bed most of the time

Day	Date MM/DD/YYYY	Total Daily Dose JAGA (mg) Given	Missed JAGA Dose (mg) & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Dose of Steriods (mg)	Name or initials of person entering information, each day
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
15											
16											
17											
18											
19											
20											
21											
22											
23											
24											
25											
26											
27											
28											
29											
30											
31											

NIH Study Team

Reviewer Name: _____ Reviewer Signature: _____ Date Reviewed: _____

JDM Diary

Date of last clinic visit: _____ **Study #:** _____ **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

Total Daily Dose _____ **(mg)**

Dose breakdown _____ **(mg)**

Dose Frequency - circle or check one. (number of doses per day)

If your dose or dose frequency changes, start a new diary page starting with the current calendar day.

- 1 time per day ☐
- 2 times per day ☐
- 3 times per day ☐
- 4 times per day ☐
- 5 times per day ☐

0 - No fever	0 - No rash	0 - No pain	0 - No headache	0 - No fatigue	0 - No muscle weakness	
1 - Fever without impact on daily activity	1 - Rash barely present	1 - Mild pain not requiring medication, no limping	1 - Mild headache not requiring medication or any adjustments of daily activities	1 - Mild fatigue, no functional impact	1 - Mild weakness	
2 - Fever requiring fever-reducing medication or with mild impact on daily	2 - Rash generally brighter pink to red	2 - Pain requiring medication or leading to limping or other mild functional	2 - Headache requiring medication or having mild functional impact	2 - Moderate fatigue with mild functional impact	2 - Moderate weakness	
3 - Fever requiring medication with significant impact on daily activities (missing school	3 - Rash generally bright red	3 - Pain requiring medication or having severe functional impact	3 - Headache requiring medication and having severe functional impact	3 - Severe fatigue with severe functional impact	3 - Severe weakness	
4 - Fever forcing the patient to be bedridden	4 - Worst rash ever	4 - Severe pain, child refusing to walk, or staying in bed most of the time	4 - Severe headache resulting in patient staying in bed most of the day or lying down due to headache	4 - Severe fatigue resulting in patient staying in bed most of the time	4 - Extremely severe weakness	

Day	Date MM/DD/YYYY	Total Daily Dose JAGA mg Given	Missed JAGA Dose & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Weakness	Dose of Steroids (mg)	Name or initials of person entering information, each day
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
13												
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25												
26												
27												
28												
29												
30												
31												

Key for scoring per symptom:

Fever	0 - 4 listed above
Rash	0 - no rash
	1 - Faint pink - involvement of a smaller area, such as joints, eyelids, and/or cheeks
	2 - Pink to red - involvement of moderate area, such as joints, face, hands, and arms,
	3 - Bright red - often with more extensive involvement of moderate area, such as joints, face, neck & shoulders, hands & arms, lower extremities, & possibly trunk or
	4 - Worst - Extremely bright red & often with itching, scratching, or with
Musculoskeletal	0 - 4 listed above
Headache	0 - 4 listed above
Fatigue	0 - 4 listed above
Weakness	0 - No weakness - Strong in all muscle groups & have no problems with their muscle strength or ability to do things compared to their peers
	1 - Mild Weakness - Almost normal strength in all muscles & can do almost everything with their muscles that their peers can do with minimal/mild problems
	2 - Moderate Weakness - Their muscles are somewhat weak; can do things with their muscles, but using their muscles for many things is hard for them)
	3 - Severe Weakness - Their muscles are very weak & using their muscles for most things is hard for them; they need assistance with some things)
	4 - Extremely Severe Weakness - Their muscles are extremely weak & using their

MIH Study Team

Name: _____

Reviewer Signature: _____

Date Reviewed: _____

SAVI Diary

Date of last clinic visit: _____ **Study #:** _____ **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

Total Daily Dose _____ **(mg)**

Dose breakdown _____ **(mg)**

Dose Frequency - circle or check one. (number of doses per day)

1 time per day ☐
2 times per day ☐
3 times per day ☐
4 times per day ☐
5 times per day ☐

If your dose or dose frequency changes, start a new diary page starting with the current calendar day.

					0 - No fever	0 - No rash	0 - No pain	0 - No fatigue	0 - No breathing problems	0 - No ulcers			
					1 - Fever without impact on daily activity	1 - Rash barely present	1 - Mild pain not requiring medication, no limping	1 - Mild fatigue, no functional impact	1 - Mild breathing problems / rapid breathing / coughing, no functional impact	1 - Few ulcers, only in 1 location and/or no drainage, no ischemia			
					2 - Fever requiring fever-reducing medication or with mild impact on daily activities	2 - Rash covering 10% of body surface area	2 - Pain requiring medication or leading to limping or other mild functional impact	2 - Moderate fatigue with mild functional impact	2 - Moderate breathing problems / rapid breathing / coughing with mild functional impact	2 - Ulcers in more than 1 location and/or with some drainage, no ischemia			
					3 - Fever requiring medication with significant impact on daily activities (missing school, tiredness)	3 - Rash covering more than 30% of body surface area	3 - Pain requiring medication or having a severe functional impact	3 - Severe fatigue with a severe functional impact	3 - Severe breathing problems / rapid breathing / coughing with a severe functional impact	3 - Ulcers in multiple locations and/or significant drainage, and/or any ischemia			
					4 - Fever forcing the patient to be bedridden	4 - Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 - Severe pain, child refusing to walk, or staying in bed most of the time	4 - Severe fatigue resulting in patient staying in bed most of the time	4 - Severe breathing problems / rapid breathing / coughing which result in patient staying in bed most of the time	4 - Severe ulcers / ischemic lesions in multiple locations			
Day	**Date MM/DD/YYYY**	**Total Daily JAGA Dose Given (mg)**	**Missed JAGA Dose & Reason**	**A.M. Temp**	**Fever**	**Rash**	**Musculo-skeletal Pain**	**Fatigue**	**Respiratory/ Breathing Symptoms**	**Ulcers / Ischemic lesions**	**Dose of Steriods (mg)**	**Peak Flows**	**Name or initials of person entering information, each day**
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
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30													
31													

NIH Study Team

Name:_____ Reviewer Signature:_____ Date Reviewed:_____

Attachment 5. Protocol I4V-MC-JAGA Bohan and Peter Criteria for the Diagnosis of Polymyositis and Dermatomyositis

Criteria for the Diagnosis of Polymyositis and Dermatomyositis[a]

Criterion	Definition
1. Symmetrical Weakness	Weakness of limb-girdle muscles and anterior neck flexors progressing over weeks to months with or without dysphagia or respiratory muscle involvement
2. Muscle Biopsy Evidence	Evidence of necrosis of Type I and II fibers, phagocytosis, regeneration with basophilia, large vesicular sarcolemmal nuclei and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size, and an inflammatory exudate, often perivascular
3. Elevation of Muscle Enzymes	Elevation in serum of skeletal muscle enzymes, particularly creatine phosphokinase and often aldolase, serum glutamate oxaloacetate, pyruvate transaminases, and lactate dehydrogenase
4. Electromyographic Evidence	Electromyographic triad of short, small, polyphasic, motor units, fibrillations, positive sharp waves, and insertional irritability, and bizarre, high-frequency, repetitive discharges
5. Dermatologic Features	A lilac discoloration of the eyelids (heliotrope) with periorbital edema, a scaly erthematous dermatitis over the dorsum of the hands (especially the metacarpophalangeal and proximal interphalangeal joints, Gottron's sign), and involvement of the knees, elbows, and medial malleoli, as well as the face, neck, and upper torso

[a] Confidence limits can be defined as follows: For a definite diagnosis of dermatomyositis, 3 of 4 criteria plus the rash must be present. For a probable diagnosis of dermatomyositis, 2 criteria plus the rash must be present. For a possible diagnosis of dermatomyositis, 1 criterion plus the rash must be present.

Data from Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med.* 1975;292(7):344–347, with permission.

Attachment 6. Protocol I4V-MC-JAGA Juvenile Dermatomyositis Core Set Measures

Core Set Measures

Domain	Core Set Measures
Global Activity	Physician global disease activity assessment by Likert or VAS Parent/patient global disease activity assessment by Likert or VAS
Muscle Strength	MMT by a 0 to 10 point or expanded 0 to 5 point scale to include proximal, distal, and axial muscles (adults and children ≥4 years of age)
Physical Function	Validated parent/patient questionnaire of activities of daily living (HAQ/CHAQ)
Laboratory Assessment	Activity of at least one serum muscle enzyme from the following: creatine kinase (CK), aldolase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)
Extramuscular Disease	A validated approach that is comprehensive and assesses cutaneous, gastrointestinal, articular, cardiac, and pulmonary activity. Myositis Disease Activity Assessment Tool has been validated.

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; HAQ = Health Assessment Questionnaire; MMT = Manual Muscle Test – 8 designated muscles; VAS = visual analog scale.

Manual Muscle Testing – 8 Designated Muscles

Muscle Groups	Right (0 – 10)	Left (0 – 10)	Axial (0 – 10)
Axial Muscles (0 – 10)			
Neck Flexors	—	—	0 – 10
Proximal Muscles (0 – 100)			
Deltoid	0 – 10	0 – 10	—
Biceps brachii	0 – 10	0 – 10	—
Gluteus maximus	0 – 10	0 – 10	—
Gluteus medius	0 – 10	0 – 10	—
Quadriceps	0 – 10	0 – 10	—
Distal Muscles (0 – 40)			
Wrist extensors	0 – 10	0 – 10	—
Ankle dorsiflexors	0 – 10	0 – 10	—
MMT-8 Score (0 – 150)	0 – 70	0 – 70	0 – 10

Abbreviations: MMT = Manual Muscle Test – 8 designated muscles.

Attachment 7. Protocol I4V-MC-JAGA Myositis Patient/Parent Global Activity Assessment

IMACS FORM 03: PATIENT/PARENT GLOBAL ACTIVITY ASSESSMENT

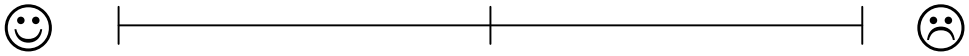
Assessor _____

Assessor's relationship to subject: Patient__; Mother:__; Father__; Other (specify):_____

Date of assessment (mm/dd/yy) _____

Your myositis is the result of the combined effects of many disease processes. One of these is disease activity, which is active inflammation in your/your child's muscles, skin, joints, intestines, heart, lungs or other parts of your body, which can improve when treated with medicines.

1. Considering all the ways that myositis affects you/your child, please rate the overall activity of your/your child's disease today by placing a mark on the line below.



No evidence of disease activity

Extremely active or severe disease activity

Attachment 8. Protocol I4V-MC-JAGA Myositis Physician's Global Activity Assessment

IMACS FORM 02: PHYSICIAN GLOBAL ACTIVITY ASSESSMENT

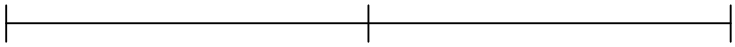
Assessor _____

Date of assessment (mm/dd/yy) _____

Physician Global Activity Assessment

Disease Activity is defined as potentially reversible pathology or physiology resulting from the myositis. Clinical findings known or suspected to be due to another disease process should not be considered in this evaluation. The global assessment of disease activity is to be judged from all the information available to you today including the subject's appearance, history, physical examination, diagnostic laboratory testing and your resultant medical therapy.

Please rate your global (overall) disease activity assessment by drawing a vertical mark on the 10-cm. line below according to the following scale: left end of line = no evidence of disease activity, midpoint of line = moderate disease activity, and right end of line = extremely active or severe disease activity.



No evidence of disease activity

Extremely active or severe disease activity

Also rate global disease activity on a 5-point Likert scale:

___0 = none
___1 = mild activity
___2 = moderate activity
___3 = severe activity
___4 = extremely severe activity

Attachment 9. Protocol I4V-MC-JAGA Myositis Disease Activity Assessment Tool

IMACS FORM 07a: Modified MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL – 2005, Version 2

ASSESSOR:_____ Date Assessed:_____

General Guidelines for Completion:

Please rate your overall (global) assessment of the ongoing **extramuscular** disease activity over the past 4 weeks on the 0-10cm VAS scale by drawing a **vertical** mark on the 10cm line according to the following guidelines:

- left end of line = no evidence of disease activity
- midpoint of line = moderate disease activity
- right end of line = extreme or maximum disease activity

* Clinical findings known or suspected to be due to another disease process or due to therapy should **NOT** be considered in this evaluation
* Disease activity is defined as a potentially reversible finding.
* Myositis or muscle disease activity should be excluded from this assessment.

Extramuscular Global Assessment	**(Absent)** **(Maximum)** __ __ . __ cm	Overall evaluation for disease activity in all extramuscular systems **(EXCLUDING MUSCLE DISEASE ACTIVITY)**

Attachment 10. Protocol Amendment I4V-MC-JAGA(s) Summary

Overview

Protocol I4V-MC-JAGA has been amended. The new protocol is indicated by amendment (s) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Literature references have been updated in the introduction (Section 5) as new information has been published about the disease states included in the program.
- The dosing rationale and dosing tables have been updated (Section 7) based on PK analyses of ongoing patients in the program.
- Wording has been clarified related to the end of the study (Section 9.6).
- BK Virus testing has been included (Section 10.2.2.7) as an additional safety measure.
- Text has been clarified in multiple sections.

Revised Protocol Sections

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

Section 1. Title Page

Study I4V-MC-JAGA is an open-label compassionate use treatment program to provide baricitinib to patients with conditions expected to benefit from JAK inhibition: CANDLE, CANDLE-related conditions, SAVI, and severe juvenile dermatomyositis. Patients will receive an initial dose based on their weight class and ~~disease type~~eGFR that may be escalated to determine a tolerable dose. Patients may be dosed for up to 288 weeks. It is anticipated that up to ~~35~~ 60 patients may be treated with baricitinib in an individualized manner. The treatment guidelines contained herein are for compassionate use only. Within these guidelines, open-label baricitinib will only be administered to patients who meet inclusion and exclusion criteria.

Section 2. Synopsis

I4V-MC-JAGA (JAGA) is an open-label compassionate use study. Patients who weigh at least 8.5 kg and who are at least 17.5 months of age are eligible to enter this study (patients who weigh less than 8.5 kg or are younger than 17.5 months may be considered for enrollment after discussion with the Sponsor). Throughout the study, the patient's disease severity will be recorded on a daily diary by the patient or patient's parent or legal guardian. Average diary scores and ongoing active clinical disease will define ~~adequate~~inadequate response to therapy and will be used to trigger changes in daily doses of baricitinib.

Number of Planned Patients/Subjects:
Entered: up to ~~35~~ 60
Enrolled: up to ~~35~~ 60
Completed: up to ~~35~~ 60

Study Design: An open-label, compassionate use treatment protocol. Patients will be treated for a maximum of 288 weeks~~.~~ followed by an optional 4 week washout period to monitor safety post treatment

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder for which there is reason to believe that JAK 1/2 inhibition will be beneficial. One such autoinflammatory disorder is chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. CANDLE syndrome typically presents ~~clinically before 6 months of age~~early in infancy with ~~fever, repeated~~ attacks of ~~erythematous and violaceous, annular cutaneous plaques, persistent periorbital erythema and edema, finger or toe swelling, hepatomegaly~~fever, panniculitis, arthritis, myositis, lipodystrophy, cytopenias, dyslipidemia, growth retardation, and variable elevation of acute-phase reactants~~. Another prominent clinical feature is progressive loss of peripheral fat (lipodystrophy).~~ Other patients eligible to

be enrolled into this study include those diagnosed with conditions related to CANDLE syndrome involving immune dysregulation: stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), an autoinflammatory syndrome with interferon (IFN) pathway dysregulation, and juvenile dermatomyositis (JDM).

Planned Duration of Treatment: ~~Each patient~~Patients may be treated up to 288 weeks.

Section 4. Abbreviations and Definitions

BID	Twice daily (divided dose two times per 24 hours)
QID	four times daily (divided dose four times per 24 hours)
TID	Three times daily (divided dose three times per 24 hours)

Section 5. Introduction

Janus-Associated Kinase Pathway and Baricitinib

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 single 5-mg doses to subjects with end stage renal disease. In patients with RA, baricitinib has also been administered at doses of up to 15 mg QD for approximately 1 month and doses up to 10 mg QD for 24 weeks. ~~A Phase~~In a phase 2b study of baricitinib in patients with RA ~~is currently ongoing. In that study~~, baricitinib at doses of up to 8 mg QD ~~will be~~were administered for up to 76 weeks.

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 et al. 2006; Henderson et al. 2010). ~~Systemic autoinflammatory~~Autoinflammatory diseases ~~comprise a group of~~ are immune dysregulatory conditions that typically present in early childhood with ~~episodic, systemic,~~fever and ~~organ~~disease-specific patterns of organ inflammation (Masters et al. 2009; Henderson et al. 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, ~~and~~ frequent fevers~~. Neutrophil~~ and neutrophil infiltration ~~into~~of the target organs ~~is characteristic of many of the autoinflammatory diseases.~~(i.e. skin).

The genetics of many of the autoinflammatory diseases ~~has~~have been elucidated over the past several years.

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 (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated

temperature) (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 patients do not respond to DMARDs, IL-1 or IL-6 blocking agents or 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). A review of mortality of all reported patients and those seen at the NIH suggests a mortality of more than 20% before the age of 30 (Kim H et al. in press)

- **CANDLE-Related Conditions.** A group of conditions that have very strong IFN response signature have recently been identified in the gene expression studies from whole blood. These conditions share clinical, pathological, and immunological features, which are different from those typically observed in IL-1-mediated autoinflammatory diseases (including NOMID, deficiency of IL-1 receptor antagonist, hyperimmunoglobulin D with periodic fever syndrome, TNF receptor-associated periodic syndrome, and familial Mediterranean fever) that respond to IL-1 inhibition. Many of the IFN~~-associated conditions~~mediated autoinflammatory diseases do not respond to IL-1 blockade and share a clinical phenotype that may include CNS manifestations (CSF pleocytosis, aseptic meningitis, white matter disease, and basal ganglia calcifications), vasculopathy (arterial hypertension, pulmonary hypertension, vascular calcifications~~ such as basal ganglia calcifications,~~ or livedo reticularis), metabolic changes (lipodystrophy, dyslipidemia, insulin resistance, or intra-abdominal fat deposition), musculoskeletal manifestations (myositis, arthralgias or arthritis, and/or panniculitis~~.~~) and hematological manifestations (i.e cytopenias). In these conditions, histologic features of immature neutrophils in the inflammatory infiltrate are commonly seen on skin biopsy~~.~~ (Canna and Goldbach-Mansky 2015).

Summary

In Study I4V-MC-JAGA (JAGA), a within-patient dose-escalation treatment regimen of baricitinib will be utilized. Patients will receive an initial dose based upon ~~their disease type and~~ weight class and eGFR. Patients ~~in the upper weight classes~~ may then have their dose escalated to determine a tolerable level.

Section 5.1.1. The Role of IL-1 in Autoinflammatory Diseases

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).

Section 5.2 CANDLE Syndrome and Related Non-IL-1 Dependent Autoinflammatory Diseases

CANDLE patients have some overlapping features with JMP patients, including a cutaneous eruption and lipodystrophy (Garg et al. 2010). Although the patients reported as JMP had more prominent joint contractures and muscle atrophy than patients described as CANDLE, the ~~difference may be due to a reporting bias. Nevertheless, the~~ detection of the same and additional mutations in PSMB8 unifies these disorders as ~~an i~~ proteasome~~-~~-associated autoinflammatory ~~syndrome.~~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 syndrome~~.~~ (Torrelo et al. 2015). In fact, 2 patients have been misdiagnosed with acute cutaneous myelogenous leukemia.

Section 7. Investigational Plan

7.1 Summary of Study Design

JAGA is an open-label compassionate use treatment program for patients who weigh at least 8.5 kg and are at least 17.5 months of age (patients who weigh less than 8.5 kg or are younger than 17.5 months may be considered for enrollment after discussion with the Sponsor). Patients will receive an initial dose based on ~~their disease type and~~ weight class and eGFR.

Screening, Initial Treatment, and Dose Escalation: Screening is a 2- to 28-day period beginning at Visit 1. After receiving written informed consent from the patient or the patient's parent or a legal guardian (hereafter, "parent" refers to "parent or legal guardian") and written assent from the patient (assent is obtained when appropriate—see Section 13.1, Obtaining Informed Consent), patients will be assigned a patient number and will be considered entered into the study and study procedures may begin. Entry procedures will be performed per the Study Schedule (Attachment 1). ~~During the screening period, patients~~Patients must complete at least ~~14 days~~2 consecutive weeks of diary entries ~~before~~prior to enrollment and receiving the first dose of baricitinib (refer to the Patient Diary and Diary Score section below). If 2 consecutive weeks of diaries, obtained as part of routine care during the 6 weeks prior to entry, are not available at Visit 1, patients can complete the 2 consecutive weeks of diary entries after study consent is signed (study entry) during the screening period, prior to enrollment. Any physical complaints/symptoms that present prior to initiation of treatment with baricitinib will be collected as preexisting conditions on the electronic case report form (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 a serious adverse event (SAE). ~~Current~~Information regarding use of concomitant medications ~~and reasons for use~~ will also be collected on the eCRF.

Baricitinib will be dosed by patient weight range and eGFR. See Table JAGA.7.1 for the dosing schedule~~.~~ for patients with eGFR ≥120 mL/min/1.73 m^2 or Table JAGA.7.2 for patients with eGFR <120 mL/min/1.73 m^2. All patients will receive an initial ~~twice~~ divided (BID or TID)-daily dose~~; patients~~. Patients may have their dose escalated~~. Patients~~, but must receive a dose

for at least 72 hours before a dose escalation can occur. Exceeding the maximum doses shown on the dosing tables is an option, but only with consensus in writing between the investigator and the Sponsor that the dose increase is in the best interest of the patient. Safety laboratory data will be assessed according to the Study Schedule (Attachment 1).

Every effort should be made to follow the dose escalation schedule shown in Table JAGA.7.1. However, if a patient's condition warrants an accelerated dose escalation schedule, this may be allowed after consultation with the Sponsor. ~~Additionally, in~~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. Where possible, these decisions should be taken following documented agreement between the investigator and ~~sponsor~~Sponsor; however, in emergency situations the investigator may take these actions. In such situations, the ~~sponsor~~Sponsor should be informed as soon as possible. Any subsequent dose restarts or increments will occur only after review of clinical data and documented agreement between the investigator and ~~sponsor~~Sponsor.

Continuing Treatment: ~~After the patient has received baricitinib at the target dose level for approximately 14 days, the patient will have an evaluation performed, which will include an assessment of the patient's clinical condition, AEs, and blood tests for safety per the Study Schedule (Attachment 1).~~ Safety laboratory assessments will be performed and reviewed by the investigator along with a copy of the patient's diary~~.~~ at visits according to the Study Schedule (Attachment 1). AEs and concomitant medications will be assessed ~~over the phone or in person by~~. Dosing will follow the ~~study team.~~ regimen shown in Table JAGA 7.1 for patients with eGFR ≥120 mL/min/1.73 m^2, and Table JAGA 7.2 for patients with eGFR <120 mL/min/1.73 m^2. Once the patient has reached a stable dose of baricitinib, the same total dose may be administered as equal or unequal divided doses ~~(administered~~. For patients with eGFR >120 mL/min/1.73 m^2 and weight <20 kg, the total daily dose can be adminstered up to 4 doses in a day ~~[~~(24 hours~~]).~~). If more than 4 doses are needed in 1 day (24 hours), then consultation and agreement with the Sponsor will be required.

1. If the patient is responding adequately to treatment (average diary score <0.5 or <1.0 [CANDLE or SAVI/JDM diary, respectively]), the patient will continue receiving baricitinib therapy with follow-up appointments according to the Study Schedule (Attachment 1). Steroid weaning may begin for patients who are receiving steroids. If the patient is responding to treatment, but has not met the threshold to begin steroid weaning and is experiencing new or worsening clinically significant adverse effects from steroids~~,~~ (including, but not limited to, cataracts, vertebral fractures due to osteoporosis, Cushinhgoid 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.

2. ~~If a patient remains unresponsive to the baricitinib dose~~2. If a patient continues to have an inadequate response to the baricitinib dose as evidenced by an elevated diary score (average diary score >0.5 or >1.0 [CANDLE or SAVI/JDM diary, respectively]) or ongoing clinical disease activity reflected by increased symptoms or elevated markers of inflammation, the dose should be increased in the dose escalation steps shown in Table JAGA.7.1~~.~~ or Table JAGA.7.2. The reason for dose increase will be documented in the medical record. Patients must have received a dose for at least 72 hours before continuing to the next dose increase. Every effort should be made to follow the dose escalation schedule shown in Table JAGA.7.1. However, if a patient's condition warrants an accelerated dose escalation schedule, this may be allowed after consultation with the Sponsor.
3. If a patient reaches the maximum allowable dose ~~(~~as specified in (Table JAGA.7.1~~)~~ or Table JAGA.7.2) and has an inadequate response to treatment, the patient may be discontinued from the study to pursue other treatment options, or one or both of the following may be considered after consultation with the Sponsor:

(1) ~~The~~Once the patient has reached a stable dose of baricitinib, the same total daily dose may be administered at greater frequency as ~~multiple~~ equal or unequal~~-~~ divided doses~~.~~ (up to 4 doses in 1 day [24 hours]).

4. If a patient ~~remains unresponsive~~continues to have an inadequate response to treatment after considering the dose modification options identified in item 3 above, then the patient will be discontinued from baricitinib. The patient will return for a follow-up safety visit approximately 28 days after their last dose of investigational product and will discontinue from the study.

Follow-up appointments will continue during the treatment period according to the Study Schedule (Attachment 1). Each patient's concomitant medications, investigational product compliance, height, weight, vital signs, and AEs will be assessed; and routine chemistry, hematology, and urinalysis assessments will be performed according to the Study Schedule (Attachment 1). A physical exam will be conducted ~~when~~according to the ~~patient completes or discontinues from the study.~~ Study Schedule (Attachment 1).

As the conditions being treated in this compassionate use program are rare, patients may be enrolled who must travel a considerable distance to the investigative site. For most of the required visits patients should be seen in-person at the investigative site. Once patients achieve a stable dose, some required visits ~~my~~may be performed as a telephone visit. If a telephone visit is performed, ~~lab~~laboratory samples should be obtained locally. Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. ~~-~~An optional 4-week washout period (Visit 801) is included to allow monitoring of patient safety after discontinuing baricitinib treatment in JAGA.

Table JAGA.7.1. Dose Escalation Schedule for Patients with eGFR ≥120 mL/min/1.73 m^2

Initial Dose

~~**Starting Dose**~~

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<~~30~~20 kg	≥120	2 mg	2 mg	2 mg	~~4~~6 mg	72 hours	0.3/NA	TID
~~50 to <60~~20-40 kg	≥120	~~6~~3 mg	—	3 mg	~~9~~6 mg	72 hours	0.15/0.3	BID
~~<30~~>40 kg	~~+2 mg~~≥120	~~2~~4 mg	—	~~2~~4 mg	~~6~~8 mg	72 hours	NA/0.2	BID

First Dose Escalation

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	≥120	2 mg	2 mg 2 mg	2 mg	8 mg	72 hours	0.4/ NA	QID
20-40 kg	≥120	3 mg	2 mg	3 mg	8 mg	72 hours	0.2/0.4	TID
>40 kg	≥120	5 mg	—	5 mg	10 mg	72 hours	NA/ 0.25	BID

Second Dose Escalation (only in patients > 40 kg)

Weight Class[a]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
>40 kg	≥120	6 mg	—	6 mg	12 mg	72 hours	NA/0.3	BID

Abbreviations: max = maximum; min = minimum; NA = not applicable.
— indicates no further dose escalation allowed.

a See Section 9.4 if a change in the patient's weight during the study would place the patient in a different weight range.

b After reaching a stable dose, the total daily dose can be administered ~~in up to 4~~ as equal or unequal divided doses.

c Duration of treatment prior to escalation includes days to obtain samples and results from safety blood test assessments prior to the first dose or first dose increase.

d Dose in mg/kg for the lowest weight and highest weight in each weight class.

Table JAGA.7.2. Dose Escalation Schedule for Patients with eGFR <120 mL/min/1.73 m^2

Initial Dose[a]

Weight Class[b]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	<120	2 mg	—	2 mg	4 mg	72 hours	0.2/NA	BID
20-40 kg	<120	2 mg	—	2mg	4 mg	72 hours	0.1/0.2	BID
>40 kg	<120	2 mg	—	2 mg	4 mg	72 hours	NA/0.1	BID

First Dose Escalation (only for patients with eGFR ≥ 60 mL/min/1.73 m^2)

Weight Class[b]	eGFR (mL/min/1.73 m^2)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Duration[c]	Min/Max Dose (mg/kg)[d]	Dosing Frequency
<20 kg	60-119	2 mg	2 mg	2 mg	6 mg	72 hours	0.3/NA	TID
20-40 kg	60-119	3 mg	—	3 mg	6 mg	72 hours	0.15/0.3	BID
>40 kg	60-119	3 mg	—	3 mg	6 mg	72 hours	NA/0.15	BID

a Baricitinib should not be used in patients with eGFR < 30 mL/min/1.73 m^2.

b See Section 9.4 if a change in the patient's weight during the study would place the patient in a different weight range.

c Duration of treatment prior to escalation includes days to obtain samples and results from safety blood test assessments prior to the first dose or first dose increase.

d Dose in mg/kg for the lowest weight and highest weight in each weight class.

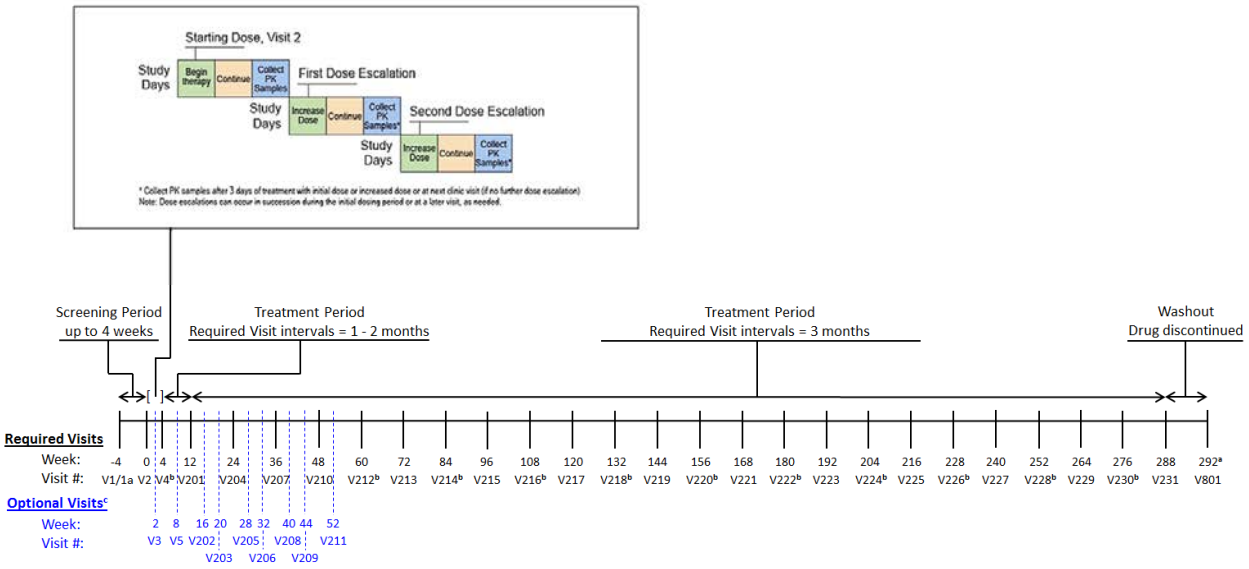


Figure JAGA.7.1. Protocol I4V-MC-JAGA study design.

Abbreviations: PK = pharmacokinetics; V = visit.

a ~~–~~ V801 (optional) should occur approximately 28 days after the last dose of investigational product.

b ~~-~~ These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, ~~lab~~laboratory samples should be obtained and tested locally~~.~~, and a copy of the laboratory report sent to the PI.

c ~~–~~ Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained ~~locally.~~ and tested locally, and a copy of the laboratory report sent to the PI.

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 (that is, CANDLE, JDM, or SAVI). The ~~assessments included in the~~ patient diaries are shown in Attachment ~~5~~4. Each patient (or caregiver) will complete the diary at approximately the same time every day during the screening period and ~~during~~for the duration of the study. Ideally, the same person will complete the diary each day. During clinic visits, it is preferable that the patient or caregiver complete the patient diary rather than site staff. ~~As this protocol will include patients with a spectrum of clinical symptoms, the investigator will determine which features listed in the diary are present and representative of the disease activity for the individual patient. Only these identified features will be used to determine average diary scores as a treatment outcome for the patient.~~

The diary is to be completed daily throughout the study. The diary score is ~~calculated after approximately 7 to 10 days of therapy at a stable dose~~used to assess disease activity and inform the need for an additional dose increase (up to the maximum allowed dose as detailed in Table JAGA.7.1) or initiation of steroid weaning as described (if the patient is receiving steroids). At each visit, the investigator will calculate the average score for each symptom being

collected on the diary (that is, the average of the daily scores since the previous visit, correcting for any day for which diary scores were not recorded). The investigator 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. An average diary score ≥0.5 (CANDLE diary) or ≥1.0 (JDM or SAVI diary) or ongoing clinical disease activity reflected by increased symptoms not captured on the diary will be indicative of a lack of complete response and will trigger a dose escalation. An average diary score <0.5 (CANDLE diary) or <1.0 (JDM or SAVI diary) will be indicative of a response to treatment and ~~will~~may trigger initiation of steroid weaning (if the patient is receiving steroids). Additionally, if the patient is responding to treatment, but has not met the average diary score threshold to begin steroid weaning and is experiencing new or worsening clinically significant adverse effects from steroids (including, but not limited to, cataracts, vertebral fractures due to osteoporosis, Cushinhgoid 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. The investigator should review the entire diary and average diary ~~score~~scores at each ~~appropriate interval~~visit. If there is a trend in the diary scores, (that is, 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.

7.2 Discussion of Design and Control

This compassionate use study is an open-label, single-arm design intended to provide baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, or severe JDM. Baricitinib has not been investigated in children; therefore, patients will receive an initial dose that may be escalated using dose escalation tables to an effective and tolerable dose. The dose-escalation period allows for safety assessments in between dose escalations. This study, by the nature of compassionate use, is not intended to answer any research hypothesis; however, it is intended to provide a potential treatment for inflammatory conditions proven resistant to other therapies. Though the open-label, single-arm design has potential for the introduction of bias, the study design represents an ethical approach for treatment of these conditions within a compassionate use framework. An optional 4-week washout period (Visit 801) is included to allow monitoring of patient safety after discontinuing baricitinib treatment in JAGA.

Continued ongoing inflammation at the organ level causes organ damage ~~resulting~~and results in significant morbidity and mortality. 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 and unsustainable chronic doses of steroids, a compassionate use study is appropriate.

Section 8. Study Population

Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder such as CANDLE syndrome, CANDLE-related syndrome, or SAVI or will have been diagnosed with severe JDM. ~~CANDLE syndrome clinically presents 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). Failure to thrive and lymphadenopathy and hypochromic or normocytic anemia can be seen (Ramot et al. 2010; Torrelo et al. 2010).~~

8.1. Inclusion Criteria

2) Have an average daily diary score of ≥0.5 (CANDLE diary) or ≥1.0 (SAVI or JDM diary) assessed over at least 2 consecutive weeks during the 6 weeks prior to entry, if available. Otherwise, patients can complete the diary after study consent is signed during the screening period and meet the inclusion criteria for enrollment into the study.

5) Have been previously treated with at least 1 biologic therapy and, in the opinion of the investigator, did not respond or are no longer responding to therapy. If the patient has been diagnosed with CANDLE~~, Nakajo-Nishimura syndrome, SAVI,~~ or an equivalent syndrome with decreased proteasome function, or SAVI, the need for previous biologic therapy is not required.

8.1.2. Patients with CANDLE-Related Conditions

46) Have organ specific inflammation involving at least one of the following: vasculopathy (such as arterial hypertension, pulmonary hypertension, vascular calcifications such as basal ganglia calcifications, or livedo reticularis), metabolic changes (such as lipodystrophy, dyslipidemia, insulin resistance, or intra-abdominal fat deposition), ~~interstitial lung disease,~~ musculoskeletal manifestations (myositis, ~~arthralgia~~arthralgias or arthritis, and/or panniculitis), hematological manifestations (i.e cytopenias) and/or interstitial lung disease.

47) Have a history of high IP-10/CXCL10 levels and/or IFN response signature in peripheral blood mononuclear cells being one of the most dysregulated blood signatures.

8.2. Exclusion Criteria

11) Are females of childbearing potential ~~(women >12 or who have had at least 1 menstrual period regardless of age) who are sexually active and~~ who do not agree to use 2 forms of highly effective ~~methods of~~ birth control ~~(see Section 8.4) or remain abstinent during~~when engaging in sexual intercourse with a male partner while enrolled in the study and for at least ~~28 days~~4 weeks following the last dose of investigational product

Females of nonchildbearing potential are defined as women ≥60 years of age, women ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, or women who are congenitally or surgically sterile (that is, have had a hysterectomy or bilateral oophorectomy or tubal ligation).

The following birth control methods are considered highly effective (the patient should choose 2 to be used with their male partner):

- oral, injectable, or implanted hormonal contraceptives
- condom with a spermicidal foam, gel, film, cream, or suppository
- occlusive cap (diaphragm or cervical/vault caps) with a spermicidal foam, gel, film, cream, or suppository
- intrauterine device
- intrauterine system (for example, progestin-releasing coil)
- vasectomized male (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate)

  Note: when local guidelines concerning highly effective methods of birth control differ from the above, the local guidelines must be followed.

12) Are ~~sexually active~~ males who do not agree to use 2 forms of highly effective birth control (see ~~Section 8.4)~~above) while engaging in sexual intercourse with female partners of childbearing potential ~~or remain abstinent during~~while enrolled in the study and for at least ~~28 days~~4 weeks following the last dose of investigational product.

19) Have had a serious systemic or local infection (including an infectious mononucleosis-like illness or herpes zoster) within 12 weeks prior to entry or during the screening period. Exceptions include SAVI patients with infected ulcerative skin lesions, which in the opinion of the investigator, would not pose an unacceptable risk for pariticipating in the study.

24) Have or have had a history of lymphoproliferative disease; or 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.

8.3.1. Inclusion Criteria for Study Enrollment

29) Have a mean daily diary score of ≥0.5 (CANDLE diary) or ≥1.0 (SAVI or JDM diary) assessed over at least 2 consecutive weeks during the 6 weeks prior to entry or after entry but prior to enrollment~~, including~~ for patients who completed the diary after consent was signed.

8.3.2. Exclusion from Study Enrollment

- Thrombocytopenia (platelets <100,000/μL). Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with a platelet count <100,000/μL if the low platelet count is considered a result of the underlying disease (see below).

8.4. Rationale for Exclusion of Certain Study Candidates

~~For Exclusion Criteria [11] and [12], each of the following is considered a single highly effective method of birth control (the patient should choose 2):~~

- ~~condom with spermicidal foam/gel/film/cream/suppository~~
- ~~occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository~~
- ~~intrauterine system (for example, progestin releasing coil)~~
- ~~vasectomized male (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)~~

8.5.2. Interruption of Investigational Product

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 the Sponsor must be contacted to discuss and document the appropriate course of action which may include a nephrology evaluation.

Table JAGA.8.1. Guidance on Interruption of Investigational Product

Hold investigational product if the following laboratory test results occur, unless continuation of investigational product is approved by the Sponsor with documentation:	If investigational product was stopped, it may be restarted after discussion with the Sponsor or when:	Additional instructions:
WBC count <~~2000~~2,000 cells/µL[a]	WBC count ≥~~2000~~2,000 cells/µL	None
ANC <~~1000~~1,000 cells/µL[a]	ANC >~~2000~~2,000 cells/µL (Patients with baseline ANC counts between 1000 and 2000 cells/µL may restart investigational product when values return to baseline.)	None
Lymphocyte count <500 cells/µL[a]	Lymphocyte count ≥500 cells/µL	None
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.)	None
eGFR <40 mL/min/1.73 m^2 (from serum creatinine)[b]	eGFR ≥40 mL/min/1.73 m^2	~~None~~Repeat BK titers in blood and urine. Nephrology evaluation may be indicated
ALT or AST >~~5x~~5 x ULN or ALT or AST >~~3x~~3 x ULN and total bilirubin >~~2x~~2 x ULN	ALT and AST return to <~~2x~~2 x ULN, and investigational product is not considered to be the cause of enzyme elevation.	See Recommended Hepatic Evaluation Guidance Document (Attachment ~~4~~3).
Hemoglobin <8 g/dL[a]	Hemoglobin ≥8 g/dL	None
HBV DNA ≥~~29 IU/mL~~[e] lower limit of quantification [c]	At the discretion of the investigator after consultation with ~~sponsor~~the Sponsor.	None
Malignancy	At the discretion of the investigator after consultation with ~~sponsor~~the Sponsor.	None
Pregnancy	At the discretion of the investigator after consultation with ~~sponsor~~the Sponsor.	None

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; ULN = upper limit of normal; WBC = white blood cell.

[c] If a HBV DNA result of 'target detected' ~~29 IU/mL or greater,~~(above the lower limit of quantification), then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study drug 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.

9.4. Rationale for Selection and Timing of Doses in the Study

Patients will receive an initial dose based on ~~their~~ weight class and ~~disease type; patients in the upper weight classes~~eGFR and may have their dose escalated to determine a tolerable dose. Dose escalation according to Table JAGA.7.1 or Table JAGA.7.2 will be performed up to the

maximum allowable dose level, as long as there are no safety concerns that would preclude increasing the dose.

~~The~~Initial dose escalation parameters ~~specified in Table JAGA.7.1 are~~were supported by PK results following baricitinib treatment of the first 2 CANDLE patients ~~(Table JAGA.9.1),~~ 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, initial improvements in clinical status were only observed upon achieving a stable 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 autoinflammatory syndromes appears to require higher concentrations of disease-modifying antirhematic drugs (Goldbach-Mansky et al. 2006) for adequate disease management. The second reason is based on the ~~current exposure data available (Table JAGA.9.1).~~generally shorter half-life of baricitinib observed in CANDLE patients in JAGA, that requires higher mg/Kg dosing in order to achieve therapeutic exposures.

With ~~Table JAGA.9.1. Preliminary Pharmacokinetics of Baricitinib in CANDLE Patients~~

~~Patient #~~	~~Clinic Visit~~	~~Dose~~	~~Hour Nominal~~	~~Concentration (ng/mL)~~	~~Concentration (nM)~~
~~CANDLE #1~~	~~V2~~	~~1 mg~~	~~1.5~~	~~2.84~~	~~6~~
~~CANDLE #1~~	~~V2~~	~~1 mg~~	~~8~~	~~4.45~~	~~10~~
~~CANDLE #1~~	~~V2~~	~~1 mg~~	~~24~~	~~0.52~~	~~1.1~~
~~CANDLE #1~~	~~V4f~~	~~2 mg~~	~~1.5~~	~~0.73~~	~~1.6~~
~~CANDLE #1~~	~~V4f~~	~~2 mg~~	~~8~~	~~15.95~~	~~34~~
~~CANDLE #1~~	~~V4f~~	~~2 mg~~	~~24~~	~~37.54~~	~~80~~
~~CANDLE #1~~	~~V6f~~	~~3 mg~~	~~1.5~~	~~36.85~~	~~79~~
~~CANDLE #1~~	~~V6f~~	~~3 mg~~	~~8~~	~~1.63~~	~~3.5~~
~~CANDLE #1~~	~~V6f~~	~~3 mg~~	~~24~~	~~4.85~~	~~10~~
~~CANDLE #2~~	~~V2~~	~~1 mg~~	~~1.5~~	~~15.86~~	~~34~~
~~CANDLE #2~~	~~V2~~	~~1 mg~~	~~8~~	~~2~~	~~4~~
~~CANDLE #2~~	~~V2~~	~~1 mg~~	~~24~~	~~< 0.40~~	~~<1~~

~~While there appear to be some inconsistencies on the time points and values indicated for Visit 4f, it is clear that, at the~~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 ~~or equal to~~ 2 mg (or 0.1 mg/kg) to approach therapeutic levels.

Subsequently, based on PK analyses of additional patients in the JAGA program, body weight and renal function (GFR estimated by the Schwartz equation for patients under 18 years and by CKD-EPI for patients older than 18 years) were identified as significant covariates on the apparent volume of distribution (V/F) and apparent clearance (CL/F), respectively, which supports dose adjustments based on weight and eGFR. Among JAGA patients with normal renal function, the observed baricitinib elimination half-life was < 6 hours in nearly all patients. The weight categories and dosing regimens presented in Table JAGA.7.1 and Table JAGA.7.2 are based on observed dose titration and stable dose in the 18 JAGA patients seen at NIH up to 04 March 2016 and the PK analyses from these patients.

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 JAGA.7.1 for patients with eGFR ≥ 120 mL/min/1.73 m^2 and Table JAGA.7.2 for patients with eGFR < 120 mL/min/1.73 m^2. If the patient loses weight during the study, the investigator may opt to keep the patient on their current dose. The investigator should ensure that the increase in weight is not related to fluid retention. ~~The dose escalation based on the new body weight should be according to Table JAGA.7.1.~~

9.5. Selection and Timing of Doses

The mean half-life of baricitinib is ~~approximately 6~~12.5 hours ~~adults~~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 STAT3-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.

10.2.1. Adverse Events

Any clinically significant findings from ECGs, ~~labs~~laboratory values, vital-sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

10.2.2. Other Safety Measures

10.2.2.7. 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 Attachment 1.

10.3.2. Samples for Drug Concentation Measurements Pharmacokinetics

Venous blood samples for the measurement of baricitinib concentrations will be collected from all patients enrolled in the study. Samples will be collected after beginning baricitinib therapy and at each dose increase at the time points shown in Table JAGA.10.1. It is also recommended that PK samples be collected more frequently for patients with eGFR < 120 mL/min/1.73 m^2, which may be at every visit if deemed necessary.

Table JAGA.14.1. Pharmacokinetic Sampling

Sampling at Beginning of Treatment and at Each Dose Increase		
Day 1, Start of therapy or day of dose increase	Baricitinib administered at initial dose or baricitinib dose increased (Table JAGA.7.1)	
Day 2	Continue baricitinib	
Day 3 or next clinic ~~visit~~[1] visit[a] (if no further dose increase)	Continue baricitinib	Collect 4 PK samples at morning dose: • Pre-morning-dose • 1 hour post-morning-dose • 1.5 hours post-morning-dose • 4 hours post-morning-dose Collect 2 PK samples at evening dose: • Pre-evening-dose • 1.5 hours post-evening-dose

Abbreviations: PK = pharmacokinetic.

[a] If PK samples cannot be processed within the specified time after collection, the PK samples may be collected on the next business day. For all PK samples, the actual date and exact timing (24-hour clock) of PK sample collection and the date, time, and dosage amount of the last 2 doses prior to the PK sample should be recorded.

PK samples must be collected each time the baricitinib dose is increased. If a patient has an adequate response to treatment at a lower dose than the maximum dose, but becomes unresponsive at a later time, the schedule of dose increases and PK sampling can be resumed. If a patient's daily dose is divided into multiple doses, an additional PK sample may be collected pre-dose for each additional dose. For example, a CANDLE patient receiving twice daily dosing who has their total daily dose divided into 3 doses may have a pre-dose PK sample collected before each of the three doses. Additional PK samples may be collected with Sponsor approval to assess safety and dosing.

For all PK samples taken, the actual date and exact timing (24-hour clock) of PK sample collection and the date and time of the last 2 doses prior to the PK sample should be recorded.

~~Plasma samples will be kept frozen at approximately –20º C to –80º C until the time of the assay. Plasma samples will be assayed for baricitinib concentration using a validated liquid chromatography with tandem mass spectrometry method at a laboratory approved by the Sponsor. PK samples may also be assayed for additional exploratory analyses. See also Section 12.2.6.1.~~

10.4. Appropriateness of Measurements

The use of the diary score as ~~a measure~~one of the measurements of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in autoinflammatory conditions conducted by investigators at the National Institutes of Health.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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, data listings will be the main tool 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.

12.2.6.1. Pharmacokinetic/Pharmacodynamic Analyses

~~PK samples are being taken to ensure drug concentrations do not exceed exposures previously studied in adults following multiple dosing.~~ Population PK analysis will be conducted to characterize PK in patients with CANDLE and SAVI. Pharmacokinetic/pharmacodynamic analyses or other analyses may also be conducted if deemed appropriate.

14. References

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Attachment 1. Protocol I4V-MC-JAGA Study Schedule

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Informed consent		X										
Demographic characteristics		X										
Height		X		X	X	X	X	X	X	X	X	X
Weight		X		X	X	X	X	X	X	X	X	X
Administer tuberculosis test		X[f]										
Read tuberculosis test			X									
Chest x-ray		X[g]										
Electrocardiogram (ECG)		X										
Review inclusion/exclusion criteria		X										
Medical history		X										
Physical examination		X		X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X	X
Assessment of JDM core measures[h]		X										
Vital signs		X		X	X	X	X	X	X	X	X	X
Diary Scores		X		X[i]	X	X	X	X	X	X	X	X
Concomitant medications		X		X	X	X	X	X	X	X	X	X
Preexisting conditions		X										

Adverse events			X	X	X	X	X	X	X	X	X

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4**[q]		**201**	**204, 207, 210**	**212**[q]**, 213, 214**[q]**, 215, 216**[q]**, 217, 218**[q]**, 219, 220**[q]**, 221, 222**[q]**, 223, 224**[q]**, 225, 226**[q]**, 227, 228**[q]**, 229, 230**[q]**, 231**	**ET**[a]	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52**[b]	**60 to 288**[c]	**−**	**292**
Number of days at visit		**28 to 2**		**Variable**[d]	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**−**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**−**	**±5**
Investigational drug dose modifications				X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]		
Investigational product returned and compliance assessed					X	X	X	X	X	X		
Laboratory												
Hematology		X		X[l]	X	X	X	X	X	X	X	X

Serum chemistry	X		X[l]	X	X	X	X	X	X	X	X
Fasting lipid panel	X					X	X	X	X	X	X
Urinalysis	X		X[l]	X	X	X	X	X	X	X	X
HBsAg, HBcAb, HBsAb	X[m]										
Hepatitis C antibody	X[m]										
HIV	X[m]										
Thyroid stimulating hormone	X[f]										
BK virus quantitative PCR, plasma	X				X		X	X[t]	X[t]	X	X
BK virus quantitative PCR, urine	X				X		X	X[t]	X[t]	X	X
Serum pregnancy test[n]	X										
Urine pregnancy test[n]			X	X	X	X	X	X	X	X	X
~~Serum~~Plasma baricitinib concentration[o]			X	X	X	X	X	X	X		
Pulmonary function tests (SAVI patients only)[p]	X		X	X	X	X	X	X	X	X	X

Abbreviations: ET = early termination; JDM = juvenile dermatomyositis; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibiody; HBsAb = hepatitis B surface antibody; HIV = human immunodeficiency virus; SAVI = STING-associated vasculopathy with onset during infancy.

a Early termination visit is required if early termination occurs.
b Visits occur at approximately 4-week intervals during Weeks 16 through 52 (including both required and optional visits)
c Visits occur at approximately 12-week intervals during Weeks 60 through 288.
d Visit 2 encompasses the initial dosing period and can vary in time depending on whether the patient progresses through the first and second dose escalation during this period. Four days is the minimum time.
e Every effort should be made to schedule patient visits within the allowable visit window; however, if a patient visit is scheduled outside the visit window, it will not be considered a protocol violation.
f If results are available from testing within 1 month, then the patient will not have to be retested.
g If a chest x-ray has not been performed in the 6 months prior to screening visit.
h Juvenile dermatomyositis patients only.
i At least 2 consecutive weeks of diary scores are required prior to beginning investigational product.
j Each time study dose is adjusted during Visit 2, this eCRF will be completed.
k See dose escalation schedule (**Table JAGA.7.1**). Each time study dose is adjusted, this eCRF will be completed. ~~Collect samples~~Samples for chemistry, hematology, and urinalysis may be collected 2 weeks after final dose increase. Collect pharmacokinetic samples as described in Section **10.3.2**.
l Collect prior to each dose escalation. Investigator will review to ensure dose escalation is appropriate. ~~Collect prior to the last dose given at Visit 2.~~
m If results are available from testing within the previous 3 months, then the patient will not have to be retested.
n 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 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.

o Baricitinib concentration samples will be collected as described in Section **10.3.2**. Samples will be collected after Visit 2 ~~only~~ if patient has a dose escalation (see **Table JAGA.7.1~~).~~**) or as needed for safety monitoring in patients with eGFR < 120 mL/min/1.73 m^2.

p Pulmonary function tests are required for SAVI patients only. Pulmonary function tests may include vital signs, pulse oximetry, imaging, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide. During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased.

q These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2.

r Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained locally.

s Optional physical exams may be performed as needed to document clinically active disease, i.e. rash, fever, arthritis, worsening of splenomegaly, hepatomegaly, and corticosteroid side effects i.e. increase in abdominal girth, cataracts, vertebral fractures due to osteoporosis, Cushinhgoid habitus, substantial weight gain, avascular necrosis, dyslipidemia, hypertension, opportunistic infections or stunted growth, hirsutism, acanthosis nigricans and others.t BK virus testing required only at on-site, required visits.

Attachment 2. Protocol I4V-MC-JAGA Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b,c]	**Serum Chemistry**[a,b]
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin[c]
Mean cell volume (MCV)	Direct bilirubin[c]
Mean cell hemoglobin concentration (MCHC)	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT/SGPT)[c]
Reticulocyte	Aspartate aminotransferase (AST/SGOT)[c]
Absolute counts of:	Blood urea nitrogen (BUN)[c]
Neutrophils, segmented	Creatinine[c]
Neutrophils, juvenile (bands)	Calcium
Lymphocytes	Glucose
Monocytes	Albumin
Eosinophils	Total protein
Basophils	Creatine phosphokinase (CPK)
Platelets	Uric acid
~~Cell Morphology~~	Gamma glutamyl transferase (GGT)
	Aldolase[d]
Lipid[e]	
Total cholesterol (TC)	
Low-density lipoprotein (LDL)	
High-density lipoprotein (HDL)	**Other Tests**[a]
Triglycerides	Hepatitis B Surface antigen (HBsAg)[g]
	Anti-Hepatitis B Core antibody (HBcAb)[g]
Urinalysis[a,b,f]	Hepatitis B Surface antibody (HBsAb)[g]
~~Color~~	Hepatitis B Virus DNA[g]
Specific gravity	Human immunodeficiency virus (HIV)[g]
pH	Hepatitis C antibody[h]
Protein	Thyroid-stimulating hormone (TSH)[g]
Glucose	Thyroxine (T4)[g]
Ketones	Pregnancy Test[i]
Bilirubin	QuantiFERON®-TB Gold[g,j]
Urobilinogen	Baricitinib serum concentration
	<u>BK virus quantitative PCR, plasma</u>
	<u>BK virus quantitative PCR, urine</u>
	<u>Urine cytology</u>
	<u>eGFR</u>
Blood	
Leukocyte esterase	
Nitrite	

Attachment 3. Protocol I4V-MC-JAGA Sampling Summary

This table summarizes the maximum number of samples and volumes for all sampling and tests during the entire 292-week study period, including the optional visits. The volume of blood drawn is less than the maximum recommended volume in both the National Institutes of Health and World Health Organization guidelines (Howie 2011) for pediatric patients. Fewer samples may actually be taken, but this will not require a protocol amendment.

	All Patients		
	Maximum Volume per Sample	**Maximum Number of Samples**	**Maximum Total Volume**
<30 kg			
— Screening laboratory tests	7 mL	1	7 mL
— Standard laboratory tests[a]	7 mL	36	252 mL
— Drug concentration[b]	1.2 mL	12	14.4 mL
Total volume of blood			**273.4 mL**
30 to <40 kg			
— Screening laboratory tests	7 mL	1	7 mL
— Standard laboratory tests[a]	7 mL	36	252 mL
— Drug concentration[b]	1.2 mL	12	14.4 mL
Total volume of blood			**273.4 mL**
40 to <50 kg			
— Screening laboratory tests	7 mL	1	7 mL
— Standard laboratory tests[a]	7 mL	37	259 mL
— Drug concentration[b]	1.2 mL	18	21.6 mL
Total volume of blood			**287.6 mL**
50 to <60 kg			
— Screening laboratory tests	7 mL	1	7 mL
— Standard laboratory tests[a]	7 mL	37	259 mL
— Drug concentration[b]	1.2 mL	18	21.6 mL
Total volume of blood			**287.6 mL**
>60 kg			
— Screening laboratory tests	7 mL	1	7 mL
— Standard laboratory tests[a]	7 mL	37	259 mL
— Drug concentration[b]	1.2 mL	18	21.6 mL
Total volume of blood			**287.6 mL**

Footnotes on next page.

[a] Standard laboratory tests include chemistry, hematology, and lipid panels.

[b] The protocol allows for additional dose escalations with sponsor consultation and approval. These potential additional dose escalations would require additional drug concentration samples not reflected here.

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1. Protocol Addendum I4V-MC-JAGA (3.1) Compassionate Use Treatment Protocol I4V-MC-JAGA(r): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Baricitinib (LY3009104)

This addendum is to be performed in addition to all procedures required by protocol I4V-MC-JAGA(r) or any subsequent amendments to that protocol.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Addendum (3) Electronically Signed and Approved by Lilly on 22-Oct-2015.
Revised Protocol Addendum (3.1) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 09-Sep-2016 GMT

2. Table of Contents

Protocol Addendum I4V-MC-JAGA (3.1) Compassionate Use Treatment Protocol I4V-MC-JAGA(r): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

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3. Rationale for Addendum

This addendum applies to sites enrolling patients with Aicardi-Goutières Syndrome (AGS). AGS is a monogenic disorder resulting from loss of function 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). Given that AGS is an interferon-mediated disease, patients with AGS are expected to benefit from JAK1 and JAK2 inhibition and, thus, it may be beneficial to treat them with baricitinib. The purpose of this addendum is to add specific entry and patient assessment criteria for patients with AGS to the existing Protocol I4V-MC-JAGA(r). The addendum is being revised in order to allow for an additional safety procedure (fundoscopy) to be completed as part of the physical examination if, in the opinion of the investigator, it is needed to monitor safety in specific AGS patients.

4. Protocol Additions

The following sections of Protocol I4V-MC-JAGA(r) have been modified in this addendum to allow patients with AGS to be eligible for enrollment at specific sites.

2. Synopsis

Number of Planned Patients/Subjects: Entered: up to 60 Enrolled: up to 60 Completed: up to 60
Objectives: The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, juvenile dermatomyositis (JDM), SAVI, or AGS results in a reduction in the patient's mean daily diary scores as follows: • CANDLE diary: reduction in mean daily score to <0.5 • SAVI diary: reduction in mean daily score to <1.0, exclusive of respiratory/breathing symptom, and a <1.0 increase from baseline in the respiratory/breathing symptom • JDM diary: decrease in mean diary score by 1 point in at least 3 categories • AGS diary: reduction in mean daily score to <0.5.
Diagnosis and Main Criteria for Inclusion and Exclusions: Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder for which there is reason to believe that JAK 1/2 inhibition will be beneficial. One such autoinflammatory disorder is chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. CANDLE syndrome 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). Other patients eligible to be enrolled into this study include those diagnosed with conditions related to CANDLE syndrome involving immune dysregulation: stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), an autoinflammatory syndrome with interferon (IFN) pathway dysregulation, juvenile dermatomyositis (JDM), and Aicardi-Goutières syndrome (AGS).

5. Introduction

The purpose of this open-label, compassionate use, treatment protocol is to provide baricitinib to patients with CANDLE*, CANDLE-related conditions, SAVI,* severe juvenile dermatomyositis (JDM), and Aicardi-Goutières syndrome (AGS) who are not responsive to biologic therapies and who require treatment with high doses of steroids to control systemic signs and symptoms of their condition (or, in the opinion of the investigator, have failed an adequate course of steroids) and are eligible for treatment under this protocol. Baricitinib is an orally administered inhibitor of Janus kinases 1 and 2 (JAK1 and JAK2).

Autoinflammatory Diseases

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

- **Aicardi-Goutières Syndrome (AGS).** 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 (for example, glaucoma, cardiomyopathy, neuropathy, endocrinological problems) in many patients. All available literature sources suggest that the prevalence of AGS is well below 5 in 10,000 persons.

Most 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 in any of the genes encoding the DNA exonuclease TREX1 (TREX1), the three non-allelic components of the RNase H2 endonuclease complex (RNASEH2A, RNASEH2B, and RNASEH2C), the deoxynucleoside triphosphate triphosphohydrolase SAMHD1 (SAMHD1), the double-stranded RNA editing enzyme ADAR (ADAR), and the double-stranded RNA cytosolic sensor IFIH1/MDA5 (IFIH1).

The proteins defective in AGS are all associated with nucleic acid metabolism/sensing. It is hypothesized that six of these proteins are involved in limiting the accumulation (TREX1, the three RNase H2 complex components, SAMHD1), or the nature (ADAR), of intracellular nucleic acid species, a failure of which process 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 interferon-stimulatory nucleic acids, and offers an elegant mechanistic explanation for the phenotypic overlap of AGS with congenital infection and systemic lupus erythematosus (SLE). 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 interferon alpha-mediated immune response and, sometimes, the production of antibodies against self-nucleic acids.

AGS is associated with increased levels of interferon alpha in the cerebrospinal fluid (CSF) and serum. However, interferon alpha levels, and white cell counts, in the CSF 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 CSF sampling, very few serial data are available (that is, systematic interferon alpha activity profiling beyond infancy has not been undertaken).

Indeed, data acquired more recently on more than 200 AGS patients using qPCR analysis of interferon stimulated genes (ISGs) indicates the presence of a so-called "interferon signature" at any age in almost 100% of patients with mutations in TREX1, RNASEH2A, RNASEH2C, SAMHD1, ADAR, and IFIH1. Around 30% of patients with RNASEH2B mutations demonstrated no such upregulation—but as ISG sampling in these studies was usually performed many years after initial diagnosis, it remains possible that all patients exhibit a positive interferon 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 life-long in most patients.

Although some children are affected by the time of birth (that is, the disease has an in utero onset), most experience the onset of disease at some point post-natally, 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, for example, 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 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 here, 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 interferons can have a neurotoxic effect at the cellular level in the absence of obvious neuroimaging changes. Most recently, IFIH1 gain of function 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.

Summary

Patients with CANDLE, CANDLE-related conditions, SAVI, severe JDM, and AGS who are not responsive to at least 1 biologic therapy (except as noted in the inclusion/exclusion criteria), and who require treatment with oral corticosteroids (≥0.15 mg/kg/day of prednisone or its equivalent) to control systemic signs and symptoms of their syndrome (or, in the opinion of the investigator, have failed an adequate course of steroids, except as noted in the inclusion/exclusion criteria), will be candidates for baricitinib treatment. 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 CANDLE, CANDLE-related conditions, SAVI, severe JDM, and AGS for whom biologics have proven to be

ineffective and/or there are no other treatments, thereby offering these patients an alternative compassionate use therapeutic option.

6. Objectives

6.1. Primary Objective

The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, JDM, or AGS results in reduction in the patient's mean daily diary scores as follows:

- CANDLE diary: reduction in mean daily score to <0.5
- SAVI diary: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and respiratory/breathing symptoms score a <1.0 increase from baseline
- JDM diary: reduction in mean score by 1 point in at least 3 categories.
- AGS diary: reduction in mean daily score to <0.5.

7. Investigational Plan

7.1. Summary of Study Design

Continuing Treatment: After the patient has received baricitinib at the target dose level for approximately 14 days, the patient will have an evaluation performed, which will include an assessment of the patient's clinical condition, AEs, and blood tests for safety per the Study Schedule. Safety laboratory assessments will be performed and reviewed by the investigator along with a copy of the patient's diary. AEs and concomitant medications will be assessed over the phone or in person by the study team. Once the patient has reached a stable dose of baricitinib, the same total dose may be administered as equal or unequal divided doses (administered up to 4 doses in a day [24 hours]). If more than 4 doses are needed in 1 day (24 hours), then consultation and agreement with the Sponsor will be required.

1. If the patient is responding adequately to treatment (average diary score <0.5 or <1.0 [CANDLE/AGS or SAVI/JDM diary, respectively]), the patient will continue receiving baricitinib therapy with follow-up appointments according to the Study Schedule. Steroid weaning may begin for patients who are receiving steroids. If the patient is responding to treatment, but has not met the threshold to begin steroid weaning and is experiencing clinically significant adverse effects from steroids, steroid weaning may begin when, in the opinion of the investigator, an adequate response has been achieved.
5. If a patient reaches the maximum allowable dose (or had a dose modification as described in item 3 above [see Protocol I4V-MC-JAGA(r)]) and his or her average diary score has decreased, but has not met the threshold for adequate response/steroid weaning (does not reach an average diary score of <0.5 or <1.0 [CANDLE/AGS or SAVI/JDM diary,

respectively]), the patient may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment.

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 (that is, CANDLE, JDM, SAVI, or AGS). The assessments included in the patient diaries are shown in Attachment 1. Each patient (or caregiver) will complete the diary at approximately the same time every day during the screening period and during the duration of the study. Ideally, the same person will complete the diary each day. During clinic visits, it is preferable that the patient or caregiver complete the patient diary rather than site staff. As this protocol will include patients with a spectrum of clinical symptoms, the investigator will determine which features listed in the diary are present and representative of the disease activity for the individual patient. Only these identified features will be used to determine average diary scores as a treatment outcome for the patient.

For patients with CANDLE, SAVI, or JDM, the patient or caregiver will be instructed to rate each symptom (fever, rash, musculoskeletal pain, and fatigue [all diaries], headache [CANDLE and JDM diaries], weakness [JDM 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]). 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. 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.

The diary is to be completed daily throughout the study. The diary score is calculated after approximately 7 to 10 days of therapy at a stable dose to assess disease activity and inform the need for an additional dose increase (up to the maximum allowed dose as detailed in the clinical protocol I4V-MC-JAGA(r)) or initiation of steroid weaning as described (if the patient is receiving steroids). At each visit, the investigator will calculate the average score for each symptom being collected on the diary (that is, the average of the daily scores since the previous visit, correcting for any day for which diary scores were not recorded). The investigator 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. An average diary score $\geq$0.5 (CANDLE or AGS diary) or $\geq$1.0 (JDM or SAVI diary) will be indicative of a lack of complete response and will trigger a dose escalation. An average diary score <0.5 (CANDLE or AGS

diary) or <1.0 (JDM or SAVI diary) will be indicative of a response to treatment and will trigger initiation of steroid weaning (if the patient is receiving steroids). The investigator should review the entire diary and diary score at each appropriate interval. If there is a trend in the diary scores, (that is, initial high scores resolve by the end of the diary period), the investigator has the option of escalating or not escalating the patient's dose of baricitinib.

Patients whose average diary scores decrease after receiving the maximum allowable dose level of baricitinib (as defined in the clinical protocol I4V-MC-JAGA(r)), but do not meet the threshold for steroid weaning (for patients receiving steroids at baseline), or an adequate response (do not reach an average daily CANDLE or AGS diary score <0.5 or a JDM or SAVI diary score <1.0), may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment. This will not be considered to be a protocol violation.

7.2. Discussion of Design and Control

This compassionate use study is an open-label, single-arm design intended to provide baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, severe JDM, or AGS. Baricitinib has not been investigated in children; therefore, patients will receive an initial dose that may be escalated using dose escalation tables to an effective and tolerable dose. The dose-escalation period allows for safety assessments in between dose escalations. This study, by the nature of compassionate use, is not intended to answer any research hypothesis; however, it is intended to provide a potential treatment for inflammatory conditions proven resistant to other therapies. Though the open-label, single-arm design has potential for the introduction of bias, the study design represents an ethical approach for treatment of these conditions within a compassionate use framework.

8. Study Population

Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder such as CANDLE syndrome, CANDLE-related syndrome, SAVI, or AGS, or will have been diagnosed with severe JDM. CANDLE syndrome clinically presents 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). Failure to thrive and lymphadenopathy and hypochromic or normocytic anemia can be seen (Ramot et al. 2010; Torrelo et al. 2010).

8.1. Inclusion Criteria

2) Have an average daily diary score of ≥0.5 (CANDLE or AGS diary) or ≥1.0 (SAVI or JDM diary) assessed over at least 2 weeks prior to entry, if available. Otherwise, patients can complete the diary after study consent is signed during the screening period and meet the inclusion criteria for enrollment into the study.

3) Are ≥17.5 months of age (or are ≥6 months of age with AGS). Patients younger than 17.5 months (or 6 months with AGS) of age can be considered for enrollment after discussion with the Sponsor.

5) Have been previously treated with at least 1 biologic therapy and, in the opinion of the investigator, did not respond or are no longer responding to therapy. If the patient has been diagnosed with CANDLE, Nakajo-Nishimura syndrome, SAVI, AGS, or an equivalent syndrome, the need for previous biologic therapy is not required.

6) Require treatment with oral corticosteroids (≥0.15 mg/kg/d of prednisone or its equivalent) for control of systemic signs and symptoms of their chronic inflammatory disease for at least 2 weeks prior to study entry, or in the opinion of the investigator, have failed an adequate course of steroids. Treatment with or failure of treatment with steroids is not required for patients with AGS.

8.1.3. Patients with Aicardi-Goutières Syndrome

Patients with AGS are eligible for entry into the study (that is, eligible to sign consent) only if they meet all of the common inclusion criteria (1 through 8 in Section 8.1 of the Clinical Protocol I4V-MC-JAGA(r)) and the following criterion:

48) A molecular diagnosis of AGS or neuroimaging and clinical findings consistent with a diagnosis of AGS.

8.3. Enrollment Criteria

8.3.1. Inclusion Criteria

29) Have a mean daily diary score of ≥0.5 (CANDLE or AGS diary) or ≥1.0 (SAVI or JDM diary) assessed over at least 2 weeks prior to enrollment, including patients who completed the diary after consent was signed.

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

10.2.2.2. 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 (Protocol Attachment 1, Study Schedule).

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

10.4. Appropriateness of Measurements

The use of the CANDLE, SAVI, or JDM diary score as a measure of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in autoinflammatory conditions conducted by investigators at the National Institutes of Health. The use of the AGS diary is based on precedent from patients treated by investigators at the Children's National Medical Center, Washington, DC.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Because this study of baricitinib is designed for compassionate use and the conditions being treated are rare, it is anticipated that only a few patients will be enrolled. The data are planned to be summarized with no formal statistical analyses. A formal sample size justification is, therefore, not needed. Sixty patients are expected to be enrolled.

14. References

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

Attachment 1. Protocol Addendum JAGA(3.1) Patient Daily Diary for AGS

Disease Activity Rating Scale				
Symptom	**Rating (Circle one)**			
Neurologic Disability	0	5	7	10
0 = Able to perform all activities of daily living independently with no restriction 5 = Able to participate in the following with some level of disability: ambulation, communication or fine motor tasks 7 = Requires functional or equipment support for any of the following: ambulation, communication or fine motor tasks 10 = Dependent for all activities of daily living and unable to ambulate, communicate or perform fine motor tasks even with support				
Crying	0	1	2	3
0 = No crying 2 = Inconsolable >2 minutes OR cry intermittently for <10 minutes 3 = Inconsolable >2 minutes AND cry intermittently for >10 minutes				
Length of Uninterrupted Sleep	0	1	2	3
0 = Sleeps more than 3 hours for infants< less than 6 months; more than 6 hours for children over 6 months 1 = Sleeps 2–3 hours at a time for infants less than 6 months; more than 4-5 hours for children over 6 months 2 = Sleeps 1–2 hours for infants less than 6 months,; more than 2-3 hours for children over 6 months 3 = Sleeps <1 hour for infants less than 6 months; greater than 1-2 hours for children over 6 months				
Generalized Seizure	0		8	
0 = No seizures 8 = Tonic-clonic, subtle staring, chewing, arching				
Fever	0		1	
0 = No fever 1 = Temp greater than or equal to 37.3°C (99.1°F)				
Excessive Irritability	0	1	2	3
1 = Consoling calms infant in 3–5 minutes 2 = Consoling calms infant in 6–15 minutes 3 = Consoling calms in >15 minutes or not at all				
Skin Findings body	0	1	2	3
0 = No rashes 1 = Blotchy red rash which comes and goes 2 = Persistently red spots which stay 3 = Persistent spots which do not blanche when pressed on				
Skin Findings hands, feet and ears	0	1	2	3
0 = No rashes 1 = Blotchy red rash which comes and goes 2 = Persistently red spots which stay 3 = Persistent spots which do not blanche when pressed on				

Attachment 2. Protocol Addendum Revisions

Overview

Protocol Addendum I4V-MC-JAGA(3) "Compassionate Use Treatment Protocol I4V-MC-JAGA(r): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis" has been revised. The revised protocol addendum is indicated by revision 3.1 and will be used in place of any preceding version of this protocol addendum.

The overall changes and rationale for the changes made to this protocol addendum are as follows:

- The addendum is being revised in order to allow for an additional safety procedure (fundoscopy) to be completed as part of the physical examination if, in the opinion of the investigator, it is needed to monitor safety in specific AGS patients.
- Minor editorial changes were also made.

Revised Protocol Addendum

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

Section 3. Rationale for Addendum

This addendum applies to sites enrolling patients with Aicardi-Goutières Syndrome (AGS). AGS is a monogenic disorder resulting from loss of function 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). Given that AGS is an interferon-mediated disease, patients with AGS are expected to benefit from JAK1 and JAK2 inhibition and, thus, it may be beneficial to treat them with baricitinib. The purpose of this addendum is to add specific entry and patient assessment criteria for patients with AGS to the existing Protocol I4V-MC-JAGA(r). The addendum is being revised in order to allow for an additional safety procedure (fundoscopy) to be completed as part of the physical examination if, in the opinion of the investigator, it is needed to monitor safety in specific AGS patients.

Section 4. Protocol Additions

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

10.2.2.2. 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 (Protocol Attachment 1, Study Schedule).

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

10.4. Appropriateness of Measurements

The use of the CANDLE, SAVI, or JDM diary score as a measure of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in autoinflammatory conditions conducted by investigators at the National Institutes of Health. The use of the AGS diary is based on precedent from patients treated by investigators at the Children's National ~~Hospital~~Medical Center, Washington, DC.

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Approver: PPD
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Signature meaning: Approved

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Approval Date & Time: 09-Sep-2016 14:59:44 GMT
Signature meaning: Approved

1. Compassionate Use Treatment Protocol I4V-MC-JAGA(r): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Confidential Information

Baricitinib (LY3009104)

Study I4V-MC-JAGA is an open-label compassionate use treatment program to provide baricitinib to patients with conditions expected to benefit from JAK inhibition: CANDLE, CANDLE-related conditions, SAVI, and severe juvenile dermatomyositis. Patients will receive an initial dose based on their weight class and disease type that may be escalated to determine a tolerable dose. Patients may be dosed for up to 288 weeks. It is anticipated that up to 35 patients may be treated with baricitinib in an individualized manner. The treatment guidelines contained herein are for compassionate use only. Within these guidelines, open-label baricitinib will only be administered to patients who meet inclusion and exclusion criteria.

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Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly: 14 October 2011.
Approval dates for Amendments (a) through (q) are shown on the following page.
Amendment (r) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 20-Feb-2015 GMT

Amendment (a) Electronically Signed and Approved by Lilly: 20 October 2011.
Amendment (b) Electronically Signed and Approved by Lilly: 15 December 2011.
Amendment (c) Electronically Signed and Approved by Lilly: 17 January 2012.
Amendment (d) Electronically Signed and Approved by Lilly: 21 February 2012.
Amendment (e) Electronically Signed and Approved by Lilly: 24 March 2012.
Amendment (f) Electronically Signed and Approved by Lilly: 08 May 2012.
Amendment (g) Electronically Signed and Approved by Lilly: 24 August 2012.
Amendment (h) Electronically Signed and Approved by Lilly: 08 September 2012.
Amendment (i) Electronically Signed and Approved by Lilly: 05 March 2013.
Amendment (j) Electronically Signed and Approved by Lilly: 03 April 2013.
Amendment (k) Electronically Signed and Approved by Lilly: 21 May 2013.
Amendment (l) Electronically Signed and Approved by Lilly: 06 August 2013.
Amendment (m) Electronically Signed and Approved by Lilly: 10 October 2013.
Amendment (n) Electronically Signed and Approved by Lilly: 05 November 2013
Amendment (o) Electronically Signed and Approved by Lilly: 09 December 2013.
Amendment (p) Electronically Signed and Approved by Lilly: 30 January 2014.
Amendment (q) Electronically Signed and Approved by Lilly: 09 May 2014.

2. Synopsis

I4V-MC-JAGA (JAGA) is an open-label compassionate use study. Patients who weigh at least 8.5 kg and who are at least 17.5 months of age are eligible to enter this study (patients who weigh less than 8.5 kg or are younger than 17.5 months may be considered for enrollment after discussion with the Sponsor). Throughout the study, the patient's disease severity will be recorded on a daily diary by the patient or patient's parent or legal guardian. Average diary scores will define adequate response to therapy and will be used to trigger changes in daily doses of baricitinib. Once a patient achieves a low average daily diary score (defined below), the investigator will begin to taper the patient's steroid dose (if the patient is receiving steroids). Patients whose average diary score decreases substantially, but who do not meet the threshold for adequate response/steroid weaning may continue in the study, if the investigator and Sponsor agree that the patient has shown favorable response to treatment with baricitinib, and that it is in the best interest of the patient to continue treatment.

Synopsis: Study I4V-MC-JAGA

Name of Investigational Product: Baricitinib	
Title of Study: Compassionate Use Treatment Protocol I4V-MC-JAGA: Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis	
Number of Planned Patients/Subjects: Entered: up to 35 Enrolled: up to 35 Completed: up to 35	**Phase of Development:** Not Applicable for Compassionate Use
Length of Study: Up to 292 weeks Planned first patient visit: Nov 2011	
Objectives: The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, juvenile dermatomyositis (JDM), or SAVI results in a reduction in the patient's mean daily diary scores as follows: • CANDLE diary: reduction in mean daily score to <0.5 • SAVI diary: reduction in mean daily score to <1.0, exclusive of respiratory/breathing symptom, and a <1.0 increase from baseline in the respiratory/breathing symptom • JDM diary: decrease in mean diary score by 1 point in at least 3 categories	
Study Design: An open-label, compassionate use treatment protocol. Patients will be treated for a maximum of 288 weeks.	
Diagnosis and Main Criteria for Inclusion and Exclusions: Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder for which there is reason to believe that JAK 1/2 inhibition will be beneficial. One such autoinflammatory disorder is chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. CANDLE syndrome 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). Other patients eligible to be enrolled into this study include those diagnosed with conditions related to CANDLE syndrome involving immune dysregulation: stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), an autoinflammatory syndrome with interferon (IFN) pathway dysregulation, and juvenile dermatomyositis (JDM).	
Investigational Product, Dosage, and Mode of Administration or Intervention: Baricitinib given orally according to the dosing tables.	
Planned Duration of Treatment: Each patient may be treated up to 288 weeks.	
Reference Therapy, Dose, and Mode of Administration or Comparative Intervention: Not applicable	
Criteria for Evaluation: Pharmacokinetics/Pharmacodynamics: Plasma samples will be obtained at specified time points. Concentrations of baricitinib will be determined by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method.	
Statistical Methods: 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, data listings will be the main tool 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.	

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and 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.
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 institutional review boards [IRBs]).
AST	aspartate aminotransferase
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
CANDLE	chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS	cryopyrin-associated periodic syndromes
cGAMP	cyclic guanosine monophosphate- adenosine monophosphate
clinical research physician (CRP)	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
compassionate use	Compassionate use programs provide investigational products to patients for the treatment of a serious or immediately life-threatening disease or condition when there is no comparable or satisfactory alternative therapy available. They may also be referred to as expanded access programs.
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.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
DEG	differentially expressed gene
ECG	electrocardiogram

Electronic case report form (eCRF)	Sometimes referred to as clinical report form. A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
effectiveness	Effectiveness is the measure of the produced effect of an intervention when carried out in a clinical environment.
eGFR	estimated glomerular filtration rate
end of the study	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.
enrollment	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
HBV	hepatitis B virus
HIV	human immunodeficiency virus
i-proteasome	immunoproteasome complex
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
IFN	interferon
IL	interleukin
institutional review board/ethical review board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
IP-10/CXCL10	interferon inducible protein 10/ C-X-C motif chemokine 10
IVIg	intravenous immune globulin
JAGA	I4V-MC-JAGA
JAK	Janus kinase
JDM	juvenile dermatomyositis
JMP	joint contractures, muscle atrophy, and panniculitis
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.

NOMID	neonatal-onset multisystem inflammatory disease
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PK	pharmacokinetic
PPD	purified protein derivative
Ps	psoriasis
PSMB8	proteasome subunit beta type-8
QD	once daily
RA	rheumatoid arthritis
requesting physician	A physician who has been granted access to investigational product on a compassionate use (or expanded access) basis as a result of an unsolicited request directed to the study sponsor. The requesting physician is responsible for the conduct of a compassionate use study at a study site. If a study is conducted by a team of individuals at a study site, the requesting physician is the responsible leader of the team. Within this protocol, the requesting physician may also be referred to as principal investigator or investigator.
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. In this study, screening involves diagnostic procedures and/or tests (for example, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
STAT	signal transducers and activators of transcription
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TNF	tumor necrosis factor
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell

Compassionate Use Treatment Protocol I4V-MC-JAGA(r) Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

5. Introduction

The purpose of this open-label, compassionate use, treatment protocol is to provide baricitinib to patients with CANDLE*, CANDLE-related conditions, SAVI,* and severe juvenile dermatomyositis (JDM) who are not responsive to biologic therapies and who require treatment with high doses of steroids to control systemic signs and symptoms of their condition (or, in the opinion of the investigator, have failed an adequate course of steroids) and are eligible for treatment under this protocol. Baricitinib is an orally administered inhibitor of Janus kinases 1 and 2 (JAK1 and JAK2).

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 active transcription factors and 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 interferons (IFNs), interleukin (IL)-2, IL-6, IL-12, IL-23, 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 (Ps) (Boy et al. 2009; Kremer et al. 2009).

Baricitinib is being investigated for the treatment of inflammatory diseases, including RA and Ps. 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 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 single 5-mg doses to subjects with end stage renal disease. In patients with RA, baricitinib has also been administered at doses of up to 15 mg QD for approximately 1 month and doses up to 10 mg QD for 24 weeks. A Phase 2b study of baricitinib in patients with RA is currently ongoing. In that study, baricitinib at doses of up to 8 mg QD will be administered for up to 76 weeks.

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* CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
SAVI = stimulator of interferon genes (STING)-associated vasculopathy with onset during infancy

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 infections and infestations system/organ class. 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 et al. 2006; Henderson et al. 2010). Systemic autoinflammatory diseases comprise a group of immune dysregulatory conditions that present with episodic, systemic, and organ-specific inflammation (Masters et al. 2009; Henderson et al. 2010). 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, and frequent fevers. Neutrophil infiltration into the target organs is characteristic of many of the autoinflammatory diseases.

The genetics of many of the autoinflammatory diseases has 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 IL-1. 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 (NOMID). Most of these diseases include fever, urticaria-like rash, and arthralgia, and are associated with gain of function mutations in the inflammasome, including, but not limited to, mutations in the NLRP3 gene (McGonagle et al. 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 [Kineret®; Biovitrum]) 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 (Arcalyst®; Regeneron) (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 mutations in the proteasome subunit beta type-8 (PSMB8) gene encoding the beta5i 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 gamma IFN, 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 (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) (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.

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 described 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. Another patient harbors a *de novo* mutation at position c.442G>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 wildtype. 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 tumor necrosis factor (TNF). The clinical phenotype and the increased IFN response gene expression in the peripheral blood suggest a gain of function resulting 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).

- **CANDLE-Related Conditions.** A group of conditions that have very strong IFN response signature have recently been identified in the gene expression studies from whole blood. These conditions share clinical, pathological, and immunological features, which are different from those typically observed in IL-1-mediated autoinflammatory diseases (including NOMID, deficiency of IL-1 receptor antagonist, hyperimmunoglobulin D with periodic fever syndrome, TNF receptor-associated periodic syndrome, and familial Mediterranean fever) that respond to IL-1 inhibition. Many of the IFN-associated conditions do not respond to IL-1 blockade and share a clinical phenotype that may include vasculopathy (hypertension, vascular calcifications such as basal ganglia calcifications, or livedo reticularis), metabolic changes (lipodystrophy, dyslipidemia, insulin resistance, or intra-abdominal fat deposition), myositis, arthralgias or arthritis, and/or panniculitis. In these conditions, histologic features of immature neutrophils in the inflammatory infiltrate are commonly seen on skin biopsy.

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.

Conditions of Immune Dysregulation – Juvenile Dermatomyositis

JDM is traditionally viewed as an autoimmune (adaptive immune) disease. Characteristic clinical signs and symptoms include fatigue, fever, symmetrical weakness of the proximal musculature, and characteristic cutaneous changes consisting of heliotrope discoloration of the eyelids, which may be accompanied by periorbital edema and erythematous papules over the extensor surfaces of joints (Gottron papules). JDM may also be associated with panniculitis-induced lipodystrophy and metabolic abnormalities, such as hyperlipidemia. Support for a diagnosis of JDM is provided by elevated serum levels of muscle enzymes and the histopathological observation of inflammatory myositis on muscle biopsy. Peripheral blood cells show a characteristic pattern of high expression of IFN regulated genes (known as an IFN signature).

JDM is the most common form of idiopathic inflammatory myopathy in children, with an average age of onset of 7 years. The incidence of JDM in the United States is between 2.5 and 4.1 per million children (Batthish and Feldman 2011). Approximately one third of JDM patients have monocyclic disease that undergoes permanent remission after treatment with standard therapeutic regimens, including corticosteroids. The remaining JDM population has polycyclic disease, a subset of which has more severe disease that is difficult to treat with associated poorer outcomes. In this latter difficult-to-treat population, corticosteroids are used in combination with other immunosuppressive therapies, including, but not limited to, cyclosporine, cyclophosphamide, and intravenous immunoglobulins. Biologic agents, such as intravenous

immunoglobulins, anti-TNF agents, and rituximab, are being used in the clinic as a treatment for the more severe subset of JDM patients (Martin et al. 2012). However, patients with severe JDM are frequently unresponsive to therapy and are unable to reduce steroid use without loss of disease control.

It is hypothesized that the pathogenesis of JDM could be explained, at least in part, by an innate immune dysregulation, suggesting that, similar to CANDLE, JDM may be, at least in part, an autoinflammatory disorder as well as an autoimmune disease as these patients exhibit activation of both innate and adaptive immunity. Patients with severe JDM and patients with CANDLE syndrome show similarity of clinical phenotype with myositis and panniculitis being a typical feature of both conditions.

Myositis-associated and -specific autoantibodies have been seen in approximately 40% of JDM patients (Khanna and Reed 2010) and vascular injury with endothelial dysfunction, complement activation, and antibody deposition on small vessels is also apparent and associated with disease progression. Consistent with the contribution of both innate and adaptive immunity to the disease process, increases in circulating IL-6 and type 1 IFN-induced chemokines, including IFN inducible protein 10/ C-X-C motif chemokine 10 (IP-10/CXCL10) and monocyte chemoattractant protein-1, have been reported in JDM patients (Bilgic et al. 2009; Greenberg 2010). Furthermore, these circulating biomarkers are correlated with global visual analog scale (VAS) scores (Bilgic et al. 2009). IL-6 and Type 1 IFNs signal through the JAK-STAT pathway, supporting a hypothesis that inhibition of this pathway could provide a viable therapeutic option.

Summary

Patients with CANDLE, CANDLE-related conditions, SAVI, and severe JDM who are not responsive to at least 1 biologic therapy (except as noted in the inclusion/exclusion criteria), and who require treatment with oral corticosteroids (≥0.15 mg/kg/day of prednisone or its equivalent) to control systemic signs and symptoms of their syndrome (or, in the opinion of the investigator, have failed an adequate course of steroids), will be candidates for baricitinib treatment. 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 CANDLE, CANDLE-related conditions, SAVI, and severe JDM for whom biologics have proven to be ineffective, thereby offering these patients an alternative compassionate use therapeutic option.

In Study I4V-MC-JAGA (JAGA), a within-patient dose-escalation treatment regimen of baricitinib will be utilized. Patients will receive an initial dose based upon their disease type and weight class. Patients in the upper weight classes may then have their dose escalated to determine a tolerable level. Short-term assessment of the potential beneficial effects of baricitinib treatment will be based on a reduction in the average daily diary score and dose of systemic steroids (if the patient is receiving steroids). If treatment with baricitinib appears to be effective, continued treatment with baricitinib may be provided under the provisions of this protocol.

The study will be conducted in compliance with the protocol, good clinical practice (GCP), and applicable regulatory requirements.

5.1. Concept of Autoinflammation

5.1.1. The Role of IL-1 in Autoinflammatory Diseases

The clinical and basic research unraveling of the CIAS1/NLRP3 inflammasome, a crucial platform to activate IL-1β and controlling its release, has revealed a key inflammatory pathway that is not only constitutively activated in CAPS, but also is 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 2011), and cholesterol crystals in coronary artery disease (Goldbach-Mansky 2009; Duewell 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.

5.2. CANDLE Syndrome and Related Non-IL-1 Dependent Autoinflammatory Diseases

An autoinflammatory disorder has recently been characterized that does not respond to treatment with IL-1, TNF, and only partially to IL-6-blocking agents (Liu et al. 2012). CANDLE syndrome 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. 2010; Torrelo et al. 2010).

In an international collaborative effort, 9 patients with the clinical diagnosis of CANDLE syndrome were studied (Liu et al. 2012). Genetic analyses showed that 7 out of 9 patients harbor genetic mutation in PSMB8 of the immunoproteasome complex (i-proteasome). After the original report of CANDLE syndrome 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 **j**oint contractures, **m**uscle atrophy, and **p**anniculitis (Garg et al. 2010). Patients with JMP were recently demonstrated to carry a mutation PSMB8 (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 JMP had more prominent joint contractures and muscle atrophy than patients described as CANDLE, the

difference may be due to a reporting bias. Nevertheless, the detection of the same and additional mutations in PSMB8 unifies these disorders as an i-proteasome associated autoinflammatory syndrome. 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 syndrome. 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).

5.3. Functional Data Supporting a Rationale to Block IFN Signaling

As mentioned above, empiric treatment with targeted agents to TNF, IL-1, and IL-6 have been unsuccessful. To characterize the inflammatory pathway and to identify therapeutic targets, the cytokine profile, transcriptome, and signaling pathways in these patients has been assessed. Interestingly, IP-10/CXCL10 serum levels, were on average over 77-fold higher than controls. The 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 NOMID, an IL-1 mediated autoinflammatory syndrome, monocytes from CANDLE patients showed stronger STAT-1 phosphorylation in response to all IFN-γ concentrations from 0.1 to 100 IU used for stimulation.

To probe further for 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 ($p<.05$), 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 IPA, 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 the patients received on the IFN-induced genes, blood samples from multiple visits were obtained in 2 patients, including 1 patient treated at different times with anti-TNF-alpha and anti-IL-6 therapy. Although temporary clinical improvement was

seen with anti-TNF-alpha and anti-IL-6 treatment (Liu et al. 2012), the "IFN signature" did not improve. IL-6 blocking therapy normalized IL-6 inducible genes and C-reactive protein 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 and STAT-5 were 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.

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

26S proteasomes are multi-subunit protein complexes critical for degradation of polyubiquitynated proteins within cells. The 20S core complex consists of 2 alpha rings and 2 beta rings, each having 7 different alpha (α) or beta (β) subunits. 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 et al. 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 polyubiquitynated 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 syndrome died of cardiac failure at the age of 47. Histological examination of skeletal muscle on autopsy revealed intramitochondrial paracrystalline inclusions and

cytoplasmic and myeloid bodies in muscle cells (Oyanagi et al. 1987). Whether the inclusions seen constitute 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.

5.5. In Vitro Evidence for Using a JAK Inhibitor

JAK kinases are critical signaling molecules mediating IFN signaling on the IFN receptors. To determine the effect of a JAK kinase 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).

6. Objectives

6.1. Primary Objective

The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, or JDM results in reduction in the patient's mean daily diary scores as follows:

- CANDLE diary: reduction in mean daily score to <0.5
- SAVI diary: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and respiratory/breathing symptoms score a <1.0 increase from baseline
- JDM diary: reduction in mean score by 1 point in at least 3 categories.

6.2. Secondary Objectives

The secondary objectives are:

- to determine, in patients receiving steroids at baseline, if administration of baricitinib to patients with CANDLE, CANDLE-related conditions, or SAVI results 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, in patients receiving steroids at baseline, if the administration of baricitinib to patients with severe JDM results in a decrease in the daily dose of corticosteroids (systemic corticosteroids <0.2 mg/kg/day oral prednisone or a decrease of at least 25% of the patient's daily dose at baseline).
- to determine if the administration of baricitinib to patients with severe JDM results in a reduction in the patient's mean diary score to <1.0.

7. Investigational Plan

7.1. Summary of Study Design

JAGA is an open-label compassionate use treatment program for patients who weigh at least 8.5 kg and are at least 17.5 months of age (patients who weigh less than 8.5 kg or are younger than 17.5 months may be considered for enrollment after discussion with the Sponsor). Patients will receive an initial dose based on their disease type and weight class. Then the dose may be escalated to determine a tolerable level. 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 steroids), as appropriate.

Screening, Initial Treatment, and Dose Escalation: Screening is a 2- to 28-day period beginning at Visit 1. After receiving written informed consent from the patient or the patient's parent or a legal guardian (hereafter, "parent" refers to "parent or legal guardian") and written assent from the patient (assent is obtained when appropriate—see Section 13.1, Obtaining Informed Consent), patients will be assigned a patient number and will be considered entered into the study and study procedures may begin. Entry procedures will be performed per the Study Schedule (Attachment 1). During the screening period, patients must complete at least 14 days of diary entries before receiving the first dose of baricitinib (refer to the Patient Diary and Diary Score section below). Any physical complaints/symptoms that present prior to initiation of treatment with baricitinib will be collected as preexisting conditions on the electronic case report form (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 a serious adverse event (SAE). Current use of concomitant medications and reasons for use will also be collected on the eCRF.

Baricitinib will be dosed by patient weight range. See Table JAGA.7.1 for the dosing schedule. All patients will receive an initial twice-daily dose; patients may have their dose escalated. Patients must receive a dose for at least 72 hours before a dose escalation can occur. Exceeding the maximum doses shown on the dosing tables is an option, but only with consensus in writing between the investigator and the Sponsor that the dose increase is in the best interest of the patient. Safety laboratory data will be assessed according to the Study Schedule (Attachment 1).

Every effort should be made to follow the dose escalation schedule shown in Table JAGA.7.1. However, if a patient's condition warrants an accelerated dose escalation schedule, this may be allowed after consultation with the Sponsor. Additionally, 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. Where possible, these decisions should be taken following documented agreement between the investigator and sponsor; however, in emergency situations the investigator may take these actions. In such situations, the sponsor should be informed as soon as possible. Any

subsequent dose restarts or increments will occur only after review of clinical data and documented agreement between the investigator and sponsor.

Pharmacokinetic Sampling: Blood samples will be collected to determine baricitinib concentrations. Samples will be collected when the patient reaches steady state at the target dose level after approximately 72 hours of treatment. Alternatively, samples may be collected at the next patient visit. Additional details on PK sampling are provided in Section 10.3.2.

Continuing Treatment: After the patient has received baricitinib at the target dose level for approximately 14 days, the patient will have an evaluation performed, which will include an assessment of the patient's clinical condition, AEs, and blood tests for safety per the Study Schedule (Attachment 1). Safety laboratory assessments will be performed and reviewed by the investigator along with a copy of the patient's diary. AEs and concomitant medications will be assessed over the phone or in person by the study team. Once the patient has reached a stable dose of baricitinib, the same total dose may be administered as equal or unequal divided doses (administered up to 4 doses in a day [24 hours]). If more than 4 doses are needed in 1 day (24 hours), then consultation and agreement with the Sponsor will be required.

1. If the patient is responding adequately to treatment (average diary score <0.5 or <1.0 [CANDLE or SAVI/JDM diary, respectively]), the patient will continue receiving baricitinib therapy with follow-up appointments according to the Study Schedule (Attachment 1). Steroid weaning may begin for patients who are receiving steroids. If the patient is responding to treatment, but has not met the threshold to begin steroid weaning and is experiencing clinically significant adverse effects from steroids, steroid weaning may begin when, in the opinion of the investigator, an adequate response has been achieved.
2. If a patient remains unresponsive to the baricitinib dose, the dose should be increased in the dose escalation steps shown in Table JAGA.7.1. Patients must have received a dose for at least 72 hours before continuing to the next dose increase. Every effort should be made to follow the dose escalation schedule shown in Table JAGA.7.1. However, if a patient's condition warrants an accelerated dose escalation schedule, this may be allowed after consultation with the Sponsor.
3. If a patient reaches the maximum allowable dose (Table JAGA.7.1) and has an inadequate response to treatment, the patient may be discontinued from the study to pursue other treatment options, or one or both of the following may be considered after consultation with the Sponsor:

    (1) The total daily dose may be administered as multiple equal or unequal divided doses.

(2) The patient's dose may be increased above the maximum dose shown in Table JAGA.7.1 if, in the opinion of the investigator, this dose increase is warranted based on the clinical assessment of the patient, evaluation of available PK data, and evaluation of renal function. The Sponsor must be consulted before the dose is increased in excess of the maximum dose shown in the dosing tables. For each affected study patient, the conclusion of this consultation must be documented in a way that confirms consensus between the investigator and the Sponsor.

4. If a patient remains unresponsive to treatment after considering the dose modification options identified in item 3 above, then the patient will be discontinued from baricitinib. The patient will return for a follow-up safety visit approximately 28 days after their last dose of investigational product and will discontinue from the study.
5. If a patient reaches the maximum allowable dose (or had a dose modification as described in item 3 above) and his or her average diary score has decreased, but has not met the threshold for adequate response/steroid weaning (does not reach an average diary score of <0.5 or <1.0 [CANDLE or SAVI/JDM diary, respectively]), the patient may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment.

Follow-up appointments will continue during the treatment period according to the Study Schedule (Attachment 1). Each patient's concomitant medications, investigational product compliance, height, weight, vital signs, and AEs will be assessed; and routine chemistry, hematology, and urinalysis assessments will be performed according to the Study Schedule (Attachment 1). A physical exam will be conducted when the patient completes or discontinues from the study.

As the conditions being treated in this compassionate use program are rare, patients may be enrolled who must travel a considerable distance to the investigative site. For most of the required visits patients should be seen in-person at the investigative site. Once patients achieve a stable dose, some required visits my be performed as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally. Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed.

Baricitinib will be provided to an individual patient for up to 288 weeks. As additional safety information is obtained from ongoing clinical trials for baricitinib, additional access to baricitinib for a longer period of time will be considered. After the trial period under this study, the Sponsor will assess the benefit/risk balance for continued access to baricitinib. If no new safety concerns are detected, this study may be amended to allow for continued dosing of baricitinib for another set period of time. Figure JAGA.7.1 illustrates the study design.

Table JAGA.7.1. Dose Escalation Schedule

Starting Dose

Weight Class[a]	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]
<30 kg	2 mg		2 mg	4 mg	72 hours
30 to <40 kg	4 mg		2 mg	6 mg	72 hours
40 to <50 kg	5 mg		2 mg	7 mg	72 hours
50 to <60 kg	6 mg		3 mg	9 mg	72 hours
≥60 kg	7 mg		3 mg	10 mg	72 hours

First Dose Escalation

Weight Class[a]	Dose Increase	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]
<30 kg	+2 mg	2 mg	2 mg	2 mg	6 mg	72 hours
30 to <40 kg	+2 mg	4 mg	—	4 mg	8 mg	—
40 to <50 kg	+2 mg	5 mg	—	4 mg	9 mg	72 hours
50 to <60 kg	+2 mg	6 mg	—	5 mg	11 mg	72 hours
≥60 kg	+2 mg	7 mg	—	5 mg	12 mg	72 hours

Second Dose Escalation

Weight Class[a]	Evening Dose Increase	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Max/Min Dose (mg/kg)[d]
<30 kg	—	—	—	—	6 mg	0.30/0.2
30 to <40 kg	—	—	—	—	8 mg	0.26/0.2
40 to <50 kg	+1 mg	5 mg	—	5 mg	10 mg	0.25/0.2
50 to <60 kg	+1 mg	6 mg	—	6 mg	12 mg	0.24/0.2
≥60 kg	+2 mg	7 mg	—	7 mg	14 mg	0.23/NA

Abbreviations: max = maximum; min = minimum; NA = not applicable.

— indicates no further dose escalation allowed.

[a] See Section 9.4 if a change in the patient's weight during the study would place the patient in a different weight range.

[b] After reaching a stable dose, the total daily dose can be administered in up to 4 divided doses.

[c] Duration of treatment prior to escalation includes days to obtain samples and results from safety blood test assessments prior to the first dose or first dose increase.

[d] Dose in mg/kg for the lowest weight and highest weight in each weight class.

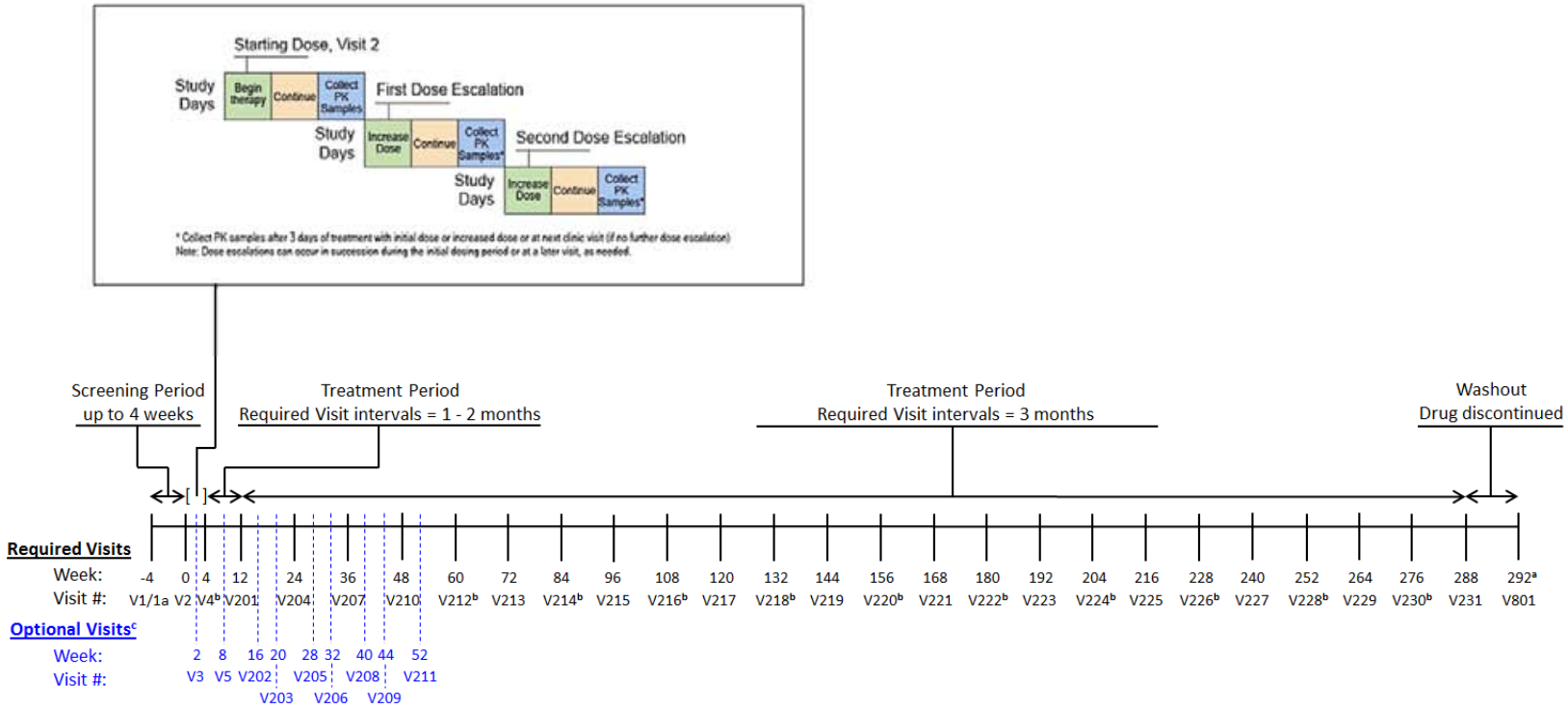

Figure JAGA.7.1. Protocol I4V-MC-JAGA study design.

Abbreviations: PK = pharmacokinetics; V = visit.

[a] V801 should occur approximately 28 days after the last dose of investigational product.

[b] These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally.

[c] Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained locally.

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 (that is, CANDLE, JDM, or SAVI). The assessments included in the patient diaries are shown in Attachment 5. Each patient (or caregiver) will complete the diary at approximately the same time every day during the screening period and during the duration of the study. Ideally, the same person will complete the diary each day. During clinic visits, it is preferable that the patient or caregiver complete the patient diary rather than site staff. As this protocol will include patients with a spectrum of clinical symptoms, the investigator will determine which features listed in the diary are present and representative of the disease activity for the individual patient. Only these identified features will be used to determine average diary scores as a treatment outcome for the patient.

The patient or caregiver will be instructed to rate each symptom (fever, rash, musculoskeletal pain, and fatigue [all diaries], headache [CANDLE and JDM diaries], weakness [JDM 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]). 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.

The diary is to be completed daily throughout the study. The diary score is calculated after approximately 7 to 10 days of therapy at a stable dose to assess disease activity and inform the need for an additional dose increase (up to the maximum allowed dose as detailed in Table JAGA.7.1) or initiation of steroid weaning as described (if the patient is receiving steroids). At each visit, the investigator will calculate the average score for each symptom being collected on the diary (that is, the average of the daily scores since the previous visit, correcting for any day for which diary scores were not recorded). The investigator 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. An average diary score $\geq$0.5 (CANDLE diary) or $\geq$1.0 (JDM or SAVI diary) will be indicative of a lack of complete response and will trigger a dose escalation. An average diary score <0.5 (CANDLE diary) or <1.0 (JDM or SAVI diary) will be indicative of a response to treatment and will trigger initiation of steroid weaning (if the patient is receiving steroids). The investigator should review the entire diary and diary score at each appropriate interval. If there is a trend in the diary scores, (that is, initial high scores resolve by the end of the diary period), the investigator has the option of escalating or not escalating the patient's dose of baricitinib.

Patients whose average diary scores decrease after receiving the maximum allowable dose level of baricitinib (as defined in Table JAGA.7.1), but do not meet the threshold for steroid weaning (for patients receiving steroids at baseline), or an adequate response (do not reach an average daily CANDLE diary score <0.5 or a JDM or SAVI diary score <1.0), may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment. This will not be considered to be a protocol violation.

7.2. Discussion of Design and Control

This compassionate use study is an open-label, single-arm design intended to provide baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, or severe JDM. Baricitinib has not been investigated in children; therefore, patients will receive an initial dose that may be escalated using dose escalation tables to an effective and tolerable dose. The dose-escalation period allows for safety assessments in between dose escalations. This study, by the nature of compassionate use, is not intended to answer any research hypothesis; however, it is intended to provide a potential treatment for inflammatory conditions proven resistant to other therapies. Though the open-label, single-arm design has potential for the introduction of bias, the study design represents an ethical approach for treatment of these conditions within a compassionate use framework.

Continued ongoing inflammation at the organ level causes organ damage resulting in significant morbidity and mortality. 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 and unsustainable chronic doses of steroids, a compassionate use study is appropriate.

8. Study Population

Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder such as CANDLE syndrome, CANDLE-related syndrome, or SAVI or will have been diagnosed with severe JDM. CANDLE syndrome clinically presents 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). Failure to thrive and lymphadenopathy and hypochromic or normocytic anemia can be seen (Ramot et al. 2010; Torrelo et al. 2010).

Patients who meet all of the inclusion criteria (Section 8.1) and do not meet any of the exclusion criteria (Section 8.2) may enter the study (that is, sign consent). In addition, patients must meet the enrollment criteria (Section 8.3) in order to be eligible to receive baricitinib. Given the severity of these diseases and the absence of other therapeutic options, any patient that does not meet inclusion, exclusion, and/or enrollment criteria may still be considered for enrollment upon consultation with the Sponsor and assessment of the benefits and risks.

8.1. Inclusion Criteria

Patients are eligible for entry into the study (that is, eligible to sign consent) only if they meet **all** of the following criteria:

1) Have systemic signs and symptoms of inflammation as manifested by the presence of 2 or more of the following symptoms: rash, fever, musculoskeletal pain, headache, fatigue, weakness, respiratory/breathing symptoms, or ulcers/ischemic lesions.

2) Have an average daily diary score of ≥0.5 (CANDLE diary) or ≥1.0 (SAVI or JDM diary) assessed over at least 2 weeks prior to entry, if available. Otherwise, patients can complete the diary after study consent is signed during the screening period and meet the inclusion criteria for enrollment into the study.

3) Are ≥17.5 months of age. Patients younger than 17.5 months of age can be considered for enrollment after discussion with the Sponsor.

4) Are ≥8.5 kg in body weight. Patients weighing less than 8.5 kg can be considered for enrollment after discussion with the Sponsor.

5) Have been previously treated with at least 1 biologic therapy and, in the opinion of the investigator, did not respond or are no longer responding to therapy. If the patient has been diagnosed with CANDLE, Nakajo-Nishimura syndrome, SAVI, or an equivalent syndrome, the need for previous biologic therapy is not required.

6) Require treatment with oral corticosteroids (≥0.15 mg/kg/d of prednisone or its equivalent) for control of systemic signs and symptoms of their chronic inflammatory disease for at least 2 weeks prior to study entry, or in the opinion of the investigator, have failed an adequate course of steroids

7) Have had previous documented elevations in acute-phase reactants (for example, high sensitivity C-reactive protein) considered to be the result of the inflammatory disease (patients with CANDLE or CANDLE-related conditions only)

8) Have the ability to provide informed consent or have a legal representative who is willing and able to provide written informed consent, provided that assent is obtained from patients at an age-appropriate level

8.1.1. Patients with Juvenile Dermatomyositis

Patients with JDM are eligible for entry into the study (that is, eligible to sign consent) only if they meet **all** of the previous criteria (1 through 8) and all of the following criteria:

37) Meet definite or probable JDM diagnosis by the criteria of Bohan and Peter (1975) (Attachment 6) with onset of first symptom prior to 18 years of age

38) Have refractory myositis as defined by the intolerance to, or an inadequate response to, corticosteroids plus an adequate regimen of at least 2 other immunomodulatory or immunosuppressive agents (including at least 1 biologic agent), such as intravenous immune globulin (IVIg), azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, tacrolimus, or cyclosporine A. Other immunomodulatory or immunosuppressive agents, such as rituximab, can be considered after discussion with the Sponsor. The definition of intolerance is side effects that require discontinuation of the medication or an underlying condition that precludes the further use of the medication.

- Adequate treatment with corticosteroids or immunosuppressive/immunomodulatory drugs is defined as the lowest of the following doses:
    - Corticosteroids: 1.0 mg/kg/d or 60 mg/d for at least 1 month
    - Azathioprine: 2 mg/kg/d or 150 mg/d for at least 3 months
    - Methotrexate: 0.3 mg/kg or 15 mg/m^2/week or 15 mg/week for at least 3 months
    - IVIg: 1 g/kg/month or 60 g/month for at least 3 months
    - Mycophenolate mofetil: 30 mg/kg/d or 1000 mg twice daily for at least 3 months
    - Cyclophosphamide: 1.0 mg/kg/d or 500 mg/m^2/month or 500 mg/month intravenously for at least 3 months

- Tacrolimus: 0.1 mg/kg/d or 5 mg/d for at least 3 months
- Cyclosporine: 2.5 mg/kg/d for at least 3 months

39) If receiving hydroxychloroquine, must have been receiving a stable dose for at least 4 weeks prior to screening visit

40) If receiving a statin, must have been receiving a stable dose for at least 8 weeks prior to screening visit

8.1.2. Patients with CANDLE-Related Conditions

Patients with CANDLE-related conditions are eligible for entry into the study (that is, eligible to sign consent) only if they meet all of the common inclusion criteria (1 through 8) and all of the following criteria:

46) Have organ specific inflammation involving at least one of the following: vasculopathy (such as hypertension, vascular calcifications such as basal ganglia calcifications, or livedo reticularis), metabolic changes (such as lipodystrophy, dyslipidemia, insulin resistance, or intra-abdominal fat deposition), interstitial lung disease, myositis, arthralgia or arthritis, and/or panniculitis.

47) Have high IP-10/CXCL10 levels and/or IFN response signature in peripheral blood mononuclear cells being one of the most dysregulated blood signatures.

8.2. Exclusion Criteria

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

9) Have received an immunosuppressive biologic agent/monoclonal antibody within 4 half-lives prior to entry, for example, anakinra (4 half-lives=18 hours); etanercept (4 half-lives=18 days); infliximab; or adalimumab (4 half-lives=36 days). Use of IVIg is permitted. Exceptions may be considered after discussion with the Sponsor.

10) Are pregnant or nursing at the time of entry

11) Are females of childbearing potential (women >12 or who have had at least 1 menstrual period regardless of age) who are sexually active and who do not agree to use 2 forms of highly effective methods of birth control (see Section 8.4) or remain abstinent during the study and for at least 28 days following the last dose of investigational product

12) Are sexually active males who do not agree to use 2 forms of highly effective birth control (see Section 8.4) with female partners of childbearing potential or remain abstinent during the study and for at least 28 days following the last dose of investigational product

13) Have had symptomatic herpes zoster infection within 12 weeks prior to entry or during the screening period

14) Have a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster, central nervous system involvement, postherpetic neuralgia)

15) Have evidence of active infection, at the time of entry or during the screening period, that in the opinion of the investigator, would pose an unacceptable risk for participating in the study

16) Have a history of active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)

17) Have documented high titer autoantibodies suggestive clinically of autoimmune diseases other than severe JDM

18) Are immunocompromised and, in the opinion of the investigator, are at an unacceptable risk for participating in the study

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

20) Have been exposed to a live vaccine within 12 weeks prior to entry or are expected to need/receive a live vaccine (including herpes zoster vaccination) during the course of the study

    Note: Investigators should review the vaccination status of their patients and follow the local guidelines for vaccination with nonlive vaccines intended to prevent infectious disease prior to entering patients into the study.

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

22) 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

23) Have an estimated glomerular filtration rate (eGFR) based on the most recent available serum creatinine of <40 mL/min/1.73 m^2

24) Have or have had a history of lymphoproliferative disease; or 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.

25) Have a history of chronic alcohol abuse or intravenous drug abuse within the 2 years prior to entry

26) Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures

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

28) Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or non-approved use of a drug or device (other than the investigational product used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

8.2.1. Patients with Juvenile Dermatomyositis

Patients with JDM will be excluded from the study if they meet **any** of the previous criteria (9 through 28) or any of the following criteria:

41) Have drug-induced myositis (myositis in patients taking medications known to induce myositis-like syndromes, including, but not limited to, statin agents, fibric acid derivatives, colchicine, and hydroxychloroquine)

42) Have a history of juvenile polymyositis, inclusion body myositis, or cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer except basal or squamous cell skin cancer or carcinoma in situ of the cervix if at least 5 years since excision

43) Have myositis in overlap with another connective tissue disease (CTD) that precludes the accurate assessment of a treatment response (for example, difficulty in assessing muscle strength in a scleroderma patient with associated myositis)

44) Have joint disease or other musculoskeletal condition, which precludes the ability to quantitate muscle strength

8.3. Enrollment Criteria

8.3.1. Inclusion Criteria

Entered patients are eligible for enrollment into the study (that is, eligible to receive baricitinib) only if they continue to meet **all** of the common inclusion criteria and applicable disease-specific inclusion criteria for entry (Section 8.1) at the time of Visit 2 plus the following requirement(s):

29) Have a mean daily diary score of ≥0.5 (CANDLE diary) or ≥1.0 (SAVI or JDM diary) assessed over at least 2 weeks prior to enrollment, including patients who completed the diary after consent was signed.

45) For JDM patients, have severe disease as assessed by core set measures (Attachment 7). Severe disease will be assessed as follows: baseline manual muscle testing (within the previous month), with a score no greater than 125 of a possible 150 in conjunction with 2 of the following abnormal core set measures:

- Parent/patient global VAS with a minimum value of 2.0 cm on a 10 cm scale (Attachment 8)
- Physician global VAS with a minimum value of 2.0 cm on a 10-cm scale (Attachment 9)
- Childhood Health Assessment Questionnaire or Health Assessment Questionnaire disability index of ≥0.25
- Elevation of at least one of the muscle enzymes (creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase [ALT], and aspartate aminotransferase [AST]) at a minimum level of 1.3 × the upper limit of normal (ULN)
- Global extramuscular disease activity score with a minimum value of 1.0 cm on a 10-cm VAS scale (this measure is the physician's composite evaluation and is based on assessments of activity scores on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac scales of the Myositis Disease Activity Assessment Tool (Attachment 10)

8.3.2. Exclusion from Study Enrollment

Entered patients are ineligible for enrollment (that is, ineligible to receive baricitinib) and should be discontinued from the study if they meet any of the following criteria:

30) Have screening laboratory test values outside the reference range for the population or investigative site that, in the opinion of the investigator, pose an unacceptable risk for the patient's participation in the study

31) Have any of the following specific abnormalities on screening laboratory tests:

- AST or ALT >2 × ULN unless the hepatitis is confirmed as resulting from the autoinflammatory condition. If autoinflammatory-associated hepatitis is present, AST or ALT cannot exceed 4 ×ULN. If inflammatory myositis is present or suspected, obtain total and direct bilirubin, aldolase, and gamma-glutamyl transferase if not yet done. Elevation in AST and/or ALT is acceptable if gamma-glutamyl transferase and total and direct bilirubin are less than 1.5 × ULN and an expert independent of the principal investigator (preferably a hepatologist or gastroenterologist) documents that the elevation is secondary to myositis. Even if inflammatory myositis is considered present, AST or ALT cannot exceed 5 × ULN.
- Hemoglobin <10 g/dL (100 g/L). Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with hemoglobin <10 g/dL if the anemia is considered a result of the underlying disease (see below).

- Total WBC count <2500 cells/μL. Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with WBC count <2500 cells/μL if the low WBC count is considered a result of the underlying disease (see below).
- Neutropenia (absolute neutrophil count [ANC] <1200 cells/μL). Patients with CANDLE, CANDLE-related conditions, or SAVI may be enrolled with an ANC <1200 cells/μL if the low ANC is considered a result of the underlying disease (see below).
- Thrombocytopenia (platelets <100,000/μL). Patients with CANDLE or SAVI may be enrolled with a platelet count <100,000/μL if the low platelet count is considered a result of the underlying disease (see below).
- eGFR <40 mL/min/1.73 m^2

Note: A patient with CANDLE, CANDLE-related condition, or SAVI may be enrolled with any of the above specific abnormalities on screening laboratory tests if these laboratory abnormalities are considered a feature of the disease. An expert independent of the principal investigator (preferably a hematologist) must evaluate the patient and, in conjunction with the principal investigator, document that the laboratory abnormality is a feature of the underlying CANDLE, CANDLE-related condition, or SAVI condition; the investigator must also consult with the Sponsor before the patient can be enrolled.

32) Have screening thyroid-stimulating hormone and/or thyroxine values outside of the laboratory's reference range and are assessed to be clinically significant. If results are available from testing within 1 month, 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, laboratory tests may be repeated once within 1 week of the initial values, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

33) 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 (for example, Bazett's corrected QT interval >450 msec for males and >470 msec for females).

34) Have evidence of active or latent TB as documented by a positive purified protein derivative (PPD) test (≥5 mm induration between approximately 2 and 3 days after application, regardless of vaccination history), medical history, and chest x-ray at screening. If results are available from testing within 1 month, then the patient will not have to be retested. Exceptions include patients with a history of latent TB who have documented evidence of completing a course of appropriate treatment:

    - If the PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active or latent TB, the patient should have a QuantiFERON®-TB Gold test. If the test is positive or indeterminate, the patient is excluded from the study.
    - The QuantiFERON®-TB Gold test may be used instead of the PPD test; patients with positive tests are excluded. If the QuantiFERON-TB Gold test is indeterminate, a retest is allowed. If the retest is also indeterminate, the patient is excluded from the study.

35) Have a positive test for hepatitis B defined as (1) positive for hepatitis B surface antigen, or (2) positive for anti-hepatitis B core antibody, but negative for hepatitis B surface antibody) unless the anti-hepatitis B core antibody is thought to be a false positive result. In the latter case, confirmation of the presence of hepatitis B virus (HBV) by DNA testing is required. An HBV DNA indeterminate result is considered HBV infection.

    If results are available from testing within the previous 3 months, then the patient will not have to be retested:

    - If any of the hepatitis B tests have an indeterminate result, confirmatory testing will be performed by an alternate method.

36) Have hepatitis C virus (positive for anti-hepatitis C antibody with confirmed presence of hepatitis C virus); have evidence of HIV infection and/or positive HIV antibodies. If results are available from testing within the previous 3 months, then the patient will not have to be retested.

Patients who are entered, but do not meet enrollment criteria, should be discontinued from the study. These patients can be re-entered into the trial (that is, be reconsented) if the investigator believes that the patient might meet enrollment criteria at a future date, taking into consideration the volume of blood required for rescreening.

8.4. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [9] excludes individuals taking medications that may confound or may interfere with the ability to assess the safety and efficacy of baricitinib. Exclusion Criteria [10] to [12] exclude individuals who are pregnant, breastfeeding, at risk for becoming pregnant, or at risk for impregnating their partner during the study. Exclusion Criteria [13] to [21] and [34] to [36] exclude individuals who are at an increased risk for infections or infectious complications. Exclusion Criteria [22] to [25] and [30] to [33] exclude individuals with concomitant medical

conditions that increase the risk for their participation in the study. Exclusion Criteria [26] to [28] exclude individuals who may not be compliant with study-related procedures or whose participation in the study may introduce bias. Exclusion Criteria [41] through [44] exclude JDM patients who may have another myositis condition that would preclude accurate muscle strength assessment.

For Exclusion Criteria [11] and [12], each of the following is considered a single highly effective method of birth control (the patient should choose 2):

- oral, injectable, or implanted hormonal contraceptives
- condom with spermicidal foam/gel/film/cream/suppository
- occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- intrauterine device
- intrauterine system (for example, progestin releasing coil)
- vasectomized male (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)

8.5. Discontinuations

8.5.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be discontinued from the investigational product, but may be allowed to continue in the study in order to provide the follow-up data. An exception may be granted in rare circumstances where the patient has a serious or life-threatening condition for which there is no effective alternative therapy and, in the opinion of the investigator, is receiving benefit from investigational product. In these rare cases, the investigator must obtain documented approval from Eli Lilly and Company (Lilly) to allow the patient to continue to receive investigational product.

8.5.2. Interruption of Investigational Product

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.

As listed in Table JAGA.8.1, certain situations necessitate a discussion with the Sponsor 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 JAGA.8.1 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 JAGA.8.1. Guidance on Interruption of Investigational Product

Hold investigational product if the following laboratory test results occur, unless continuation of investigational product is approved by the Sponsor with documentation:	If investigational product was stopped, it may be restarted after discussion with the Sponsor or when:	Additional instructions:
WBC count <2000 cells/μL[a]	WBC count ≥2000 cells/μL	None
ANC <1000 cells/μL[a]	ANC >2000 cells/μL (Patients with baseline ANC counts between 1000 and 2000 cells/μL may restart investigational product when values return to baseline.)	None
Lymphocyte count <500 cells/μL[a]	Lymphocyte count ≥500 cells/μL	None
Platelet count <75,000/μL[a]	Platelet count >100,000/μL	None
eGFR <40 mL/min/1.73 m^2 (from serum creatinine)[b]	eGFR ≥40 mL/min/1.73 m^2	None
ALT or AST >5x ULN or ALT or AST >3x ULN and total bilirubin >2x ULN	ALT and AST return to <2x ULN, and investigational product is not considered to be the cause of enzyme elevation.	See Recommended Hepatic Evaluation Guidance Document (Attachment 4).
Hemoglobin <8 g/dL[a]	Hemoglobin ≥8 g/dL	None
HBV DNA ≥29 IU/mL[c]	At the discretion of the investigator after consultation with sponsor.	None
Malignancy	At the discretion of the investigator after consultation with sponsor.	None
Pregnancy	At the discretion of the investigator after consultation with sponsor.	None

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; ULN = upper limit of normal; 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. An expert independent of the principal investigator (preferably a hematologist) must evaluate the patient and, in conjunction with the principal investigator, determine and document that the laboratory abnormality is related to the underlying disease; the investigator must also consult with the Sponsor 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 the Sponsor, 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 pre-existing renal impairment, a lower threshold for interruption may be considered after discussion with the Sponsor.

[c] If a HBV DNA result of 'target detected' 29 IU/mL or greater, then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study drug 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.

8.5.2.1. Discontinuation from Investigational Product

Any patient who is permanently discontinued from investigational product for an abnormal laboratory result should have the abnormal laboratory result reported as an AE, or an SAE if the laboratory abnormality results in an outcome requiring the AE to be reported as an SAE.

In addition, patients may be discontinued from the investigational product or from the study 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.
  - 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.
    - It is possible that a JAK inhibitor similar to Lilly's baricitinib may become commercially available before baricitinib. Once a JAK inhibitor becomes commercially available, Lilly's compassionate use program for baricitinib may be discontinued. Should another medication with potential to treat this patient population become commercially available before Lilly's baricitinib, the compassionate use program for baricitinib may be discontinued.
    - 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.
- Adverse Event
  - The investigator decides that the patient should be withdrawn. If this decision is made because of an SAE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations Section 10.2.

Patients who discontinue the investigational product and/or study early will have end-of-study procedures performed as shown in the Study Schedule (Attachment 1).

8.5.3. Discontinuation of Study Sites

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

8.5.4. 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.

9. Treatment

9.1. Treatments Administered

All eligible patients will receive treatment with baricitinib as a twice-daily dose or multiple divided doses (as described in Section 7.1). Depending upon the prescribed dose and/or the visit number, the dosing will occur during the patient's clinic visit, or packaged baricitinib will be dispensed to the patient to provide enough medication for dosing until the next visit.

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the patient, parent, or legal guardian, verifying that instructions are followed properly, maintaining accurate records of investigational product dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

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

9.2. Materials and Supplies

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

During clinic visits, investigational product may be prepared by a pharmacist or other qualified person using good pharmacy practices. Tablets are not to be split for the purpose of dose adjustment.

Investigational product will be dispensed to the patient at the investigator's study site. As needed, preparation instructions will be provided by the clinical site. Investigational product packaging will be labeled with a unique identifier for drug accountability. Investigational product will be dispensed with additional tablets to allow for sufficient supply.

9.3. Method of Assignment to Treatment

All patients participating in this study will receive open-label baricitinib.

9.4. Rationale for Selection of Doses in the Study

Patients will receive an initial dose based on their weight class and disease type; patients in the upper weight classes may have their dose escalated to determine a tolerable dose. Dose escalation according to Table JAGA.7.1 will be performed up to the maximum allowable dose level, as long as there are no safety concerns that would preclude increasing the dose.

The dose escalation parameters specified in Table JAGA.7.1 are supported by PK results following baricitinib treatment of the first 2 CANDLE patients (Table JAGA.9.1), 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, improvements in clinical status were only observed upon achieving a stable 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 autoinflammatory syndromes appears to require higher concentrations of disease-modifying antirhematic drugs (Goldbach-Mansky et al. 2006) for adequate disease management. The second reason is based on the current exposure data available (Table JAGA.9.1).

Table JAGA.9.1. Preliminary Pharmacokinetics of Baricitinib in CANDLE Patients

Patient #	Clinic Visit	Dose	Hour Nominal	Concentration (ng/mL)	Concentration (nM)
CANDLE #1	V2	1 mg	1.5	2.84	6
CANDLE #1	V2	1 mg	8	4.45	10
CANDLE #1	V2	1 mg	24	0.52	1.1
CANDLE #1	V4f	2 mg	1.5	0.73	1.6
CANDLE #1	V4f	2 mg	8	15.95	34
CANDLE #1	V4f	2 mg	24	37.54	80
CANDLE #1	V6f	3 mg	1.5	36.85	79
CANDLE #1	V6f	3 mg	8	1.63	3.5
CANDLE #1	V6f	3 mg	24	4.85	10
CANDLE #2	V2	1 mg	1.5	15.86	34
CANDLE #2	V2	1 mg	8	2	4
CANDLE #2	V2	1 mg	24	< 0.40	<1

While there appear to be some inconsistencies on the time points and values indicated for Visit 4f, it is clear that, at the 1 mg dose, the assumed maximal concentration at 1.5 hours is between 10 and 40 nM based on the 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 or equal to 2 mg (or 0.1 mg/kg) to approach therapeutic levels.

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. If the patient loses weight during the study, the investigator may opt to keep the patient on their current dose. The investigator should ensure that the increase in weight is not related to fluid retention. The dose escalation based on the new body weight should be according to Table JAGA.7.1.

9.5. Selection and Timing of Doses

The half-life of baricitinib is approximately 6 hours in adults. 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 STAT3-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.

9.6. Continued Access to Investigational Product

Patients may receive baricitinib for up to 288 weeks under the terms of this study.

This study may be terminated at the time of United States commercial availability of baricitinib or at the time of United States commercial availability of a similar JAK inhibitor or another drug with potential to treat these patients. Baricitinib will no longer be supplied if Lilly stops development of baricitinib for any reason at any time.

9.7. Blinding

This is an open-label study.

9.8. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication eCRF.

9.9. Treatment Compliance

Patient compliance with investigational product will be assessed at each visit. Compliance will be assessed by counting returned tablets. 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.

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Primary Effectiveness Measure

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

10.2. Safety Evaluations

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.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that cause patients to discontinue before completing the study. The patients should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

10.2.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to investigational product or drug-delivery system should be reported. Data on fetal outcome and breast feeding are collected for regulatory reporting and drug-safety evaluation.

Study-site personnel will record the occurrence and nature of each patient's preexisting conditions, including autoinflammatory diseases under treatment in the study.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to study procedures are reported to Lilly or designee.

In addition, all AEs occurring after the patient receives the first dose of investigational product must be reported to Lilly or its designee via eCRFs.

Any clinically significant findings from ECGs, labs, vital-sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to study procedure, studied disease state, investigational product, and/or drug-delivery system via the eCRF.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study-site personnel must clearly report to Lilly or its designee via the eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.2.1.1. Serious Adverse Events

SAE collection begins after the patient has signed informed consent and has received investigational product. If a patient experiences an SAE after signing informed consent, but prior to receiving investigational product, the event will NOT be collected unless the investigator feels the event may have been caused by a study procedure.

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

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. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs occurring after a patient has taken the last dose of investigational product will be collected in the pharmacovigilance system and the clinical data-collection database for 28 days after the last dose of investigational product, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either investigational product, or drug delivery system, or a study procedure.

SAEs that could be expected in the study population independent of drug exposure will be assessed by the Sponsor in aggregate periodically during the course of the trial are not currently defined.

10.2.1.1.1. 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 recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance documents.

10.2.1.2. Adverse Events of Special Interest

Adverse events of special interest include the following:

- infections
- myelosuppressive events of anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia
- thrombocytosis
- elevations in ALT/AST (>3 times ULN) with total bilirubin (>2 times ULN)

Patients with these events will be identified using the same criteria presented in Section 8.5.2 for the interruption of investigational product (Table JAGA.8.1) with the exception of anemia, which will be defined as a hemoglobin <6.5 g/dL, and thrombocytosis, which will be defined as a platelet count >600,000/µL.

10.2.2. Other Safety Measures

10.2.2.1. Electrocardiograms

Twelve-lead ECGs will be obtained according to the Study Schedule (Attachment 1). A single 12-lead ECG measurement will be performed at screening. This screening ECG will be interpreted by a qualified physician (the investigator or qualified designee) at the site to determine whether the patient meets entry criteria.

10.2.2.2. 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 (Attachment 1).

10.2.2.3. Vital Signs

Vital signs (blood pressure and pulse) will be measured at times indicated in the Study Schedule (Attachment 1). 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.

10.2.2.4. Chest X-Ray and Tuberculosis Testing

A posterior-anterior view chest x-ray will be obtained, unless results from a chest x-ray obtained within 6 months prior to the study are available and are either normal or show only stable

disease. The chest x-ray will be reviewed by the investigator or his/her designee to exclude patients with active TB infection.

In addition, patients will be tested at screening for evidence of active or latent TB indicated by a positive PPD TB skin test response (≥5 mm induration, between approximately 2 and 3 days after test application [visits as indicated on the Study Schedule, Attachment 1], regardless of Bacille Calmette-Guérin vaccination history). If the QuantiFERON-TB Gold test is available and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may be used instead of the PPD TB test (positive tests excluded) and may be read locally. If the QuantiFERON-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

Patients who have a documented history of completing an appropriate TB treatment regimen with no history of re-exposure since their treatment was completed are eligible to participate in the study.

10.2.2.5. Liver-Function Monitoring

Liver-function monitoring will occur frequently throughout the study. If elevations in ALT/AST or total bilirubin occur, the patient should be closely observed as described in Table JAGA.8.1 and the Recommended Hepatic Evaluation Guidance Document (Attachment 4).

10.2.2.6. 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, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide. During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased. See Attachment 1 for frequency of pulmonary function monitoring.

10.2.3. Safety Monitoring

Lilly will review SAEs within time frames mandated by company procedures. 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 8.5 for discontinuation criteria related to specific AEs.

Vitals signs will be monitored as indicated in the Study Schedule (Attachment 1).

Twelve-lead ECGs will be reviewed for safety. In addition, unscheduled ECGs may be recorded for safety assessments, if clinically indicated.

10.2.4. Complaint Handling

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

Complaints related to unblinded concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.3. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study.

Attachment 3 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study. Fewer invasive sampling may actually occur, but this will not require a protocol amendment.

10.3.1. Samples for Standard Laboratory Testing

Blood and urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, including chemistry, hematology, and urinalysis panels, will be performed. Every effort should be made to obtain all laboratory tests listed in Attachment 2; however, if laboratory tests are not available locally or test results are otherwise missing, this will not be considered a protocol violation. A pregnancy test will be performed (if applicable). Attachment 2 lists the specific tests that will be performed for this study.

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.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.3.2. Samples for Drug Concentration Measurements Pharmacokinetics

Venous blood samples for the measurement of baricitinib concentrations will be collected from all patients enrolled in the study. Samples will be collected after beginning baricitinib therapy and at each dose increase at the time points shown in Table JAGA.10.1.

Table JAGA.10.1. Pharmacokinetic Sampling

Sampling at Beginning of Treatment and at Each Dose Increase		
Day 1, Start of therapy or day of dose increase	Baricitinib administered at initial dose or baricitinib dose increased (Table JAGA.7.1)	
Day 2	Continue baricitinib	
Day 3 or next clinic visit[1] (if no further dose increase)	Continue baricitinib	Collect 4 PK samples at morning dose: • Pre-morning-dose • 1 hour post-morning-dose • 1.5 hours post-morning-dose • 4 hours post-morning-dose Collect 2 PK samples at evening dose: • Pre-evening-dose • 1.5 hours post-evening-dose

Abbreviations: PK = pharmacokinetic.

[1] If PK samples cannot be processed within the specified time after collection, the PK samples may be collected on the next business day. For all PK samples, the actual date and exact timing (24-hour clock) of PK sample collection and the date, time, and dosage amount of the last 2 doses prior to the PK sample should be recorded.

PK samples must be collected each time the baricitinib dose is increased. If a patient has an adequate response to treatment at a lower dose than the maximum dose, but becomes unresponsive at a later time, the schedule of dose increases and PK sampling can be resumed. If a patient's daily dose is divided into multiple doses, an additional PK sample may be collected pre-dose for each additional dose. For example, a CANDLE patient receiving twice daily dosing who has their total daily dose divided into 3 doses may have a pre-dose PK sample collected before each of the three doses.

For all PK samples taken, the actual date and exact timing (24-hour clock) of PK sample collection and the date and time of the last 2 doses prior to the PK sample should be recorded.

Plasma samples will be kept frozen at approximately –20º C to –80º C until the time of the assay. Plasma samples will be assayed for baricitinib concentration using a validated liquid chromatography with tandem mass spectrometry method at a laboratory approved by the Sponsor. PK samples may also be assayed for additional exploratory analyses. See also Section 12.2.6.1.

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

If the blood volumes required for PK sampling exceed established local guidelines for phlebotomy, then the PK sample collection may be modified.

10.4. Appropriateness of Measurements

The use of the diary score as a measure of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in autoinflammatory conditions conducted by investigators at the National Institutes of Health.

11. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, 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 eCRF data and use standard computer edits to detect errors in data collection

In addition, Lilly or its representatives may 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.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the Sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

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

eCRF data will be encoded and stored in a clinical trial database.

Any data for which paper documentation provided by the patient or parent 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 or parent may include, for example, a paper diary to collect patient-reported outcome measures (for example, a rating scale), a daily dosing schedule, or an event diary.

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Because this study of baricitinib is designed for compassionate use and the conditions being treated are rare, there is no minimum or maximum requirement of the number of patients to be studied.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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, data listings will be the main tool 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.

12.2.2. Patient Disposition

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

12.2.3. Patient Characteristics

A summary and list of demographic information and baseline characteristics of all enrolled patients will be created. Special care will be taken not to include sensitive personal health information that may reveal the identity of the patients.

12.2.4. 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.

12.2.5. Primary Outcome and Methodology

The primary data presentation will be a summary of the percent of patients achieving a decrease in the appropriate diary score. Additional summaries and by-patient listings of the baseline and final steroid doses and displays of changes over time may be created for those patients receiving steroids. No formal statistical test of any hypothesis will be conducted.

12.2.6. Efficacy

A by-patient listing that includes the maximum baricitinib dose received by the patient, the maximum decrease in daily corticosteroid dose for those patients receiving steroids at baseline, and the minimum patient diary score achieved while receiving the maximum baricitinib dose, the reason for discontinuation, and the nature of AEs deemed possibly related to investigational product that were experienced by the patient will be created. Additional data displays and

listings of efficacy measures over time once the patient reaches his/her maximum dose of baricitinib will be created if a sufficient number of patients are enrolled.

12.2.6.1. Pharmacokinetic/Pharmacodynamic Analyses

PK samples are being taken to ensure drug concentrations do not exceed exposures previously studied in adults following multiple dosing. Population PK analysis will be conducted to characterize PK in patients with CANDLE and SAVI. Pharmacokinetic/pharmacodynamic analyses or other analyses may also be conducted if deemed appropriate.

12.2.7. Safety Analyses

Safety measures will be summarized and/or listed. Standard listings will include TEAEs, SAEs, and results from laboratory tests for each patient. By definition, TEAEs are AEs that begin or increase in severity after the patient receives the first dose of baricitinib. If a sufficient number of patients are enrolled, 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.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient or parent understands the potential risks and benefits of participating in the study, including answering any questions the patient or parent may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient or parent in simple terms before the patient is entered into the study, and to document that the patient or parent is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of investigational product.

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 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 majority 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.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonization guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

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 current Investigator's Brochure or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

(1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines

(2) the International Conference on Harmonization GCP Guideline [E6]

(3) applicable laws and regulations

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

All or some of the obligations of the Sponsor may be assigned to a third-party organization.

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.

13.3.1. Investigator Information

Physicians with a specialty in rheumatology with access to hospitals with appropriate pharmacy support and outpatient management will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

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

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

13.3.3. Final Report Signature

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

The Sponsor's responsible medical officer will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol I4V-MC-JAGA Study Schedule

Study Schedule, Protocol I4V-MC-JAGA

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Informed consent		X										
Demographic characteristics		X										
Height		X		X	X	X	X	X	X	X	X	X
Weight		X		X	X	X	X	X	X	X	X	X
Administer tuberculosis test		X[f]										
Read tuberculosis test			X									
Chest x-ray		X[g]										
Electrocardiogram (ECG)		X										
Review inclusion/exclusion criteria		X										
Medical history		X										
Physical examination		X										
Assessment of JDM core measures[h]		X										
Vital signs		X		X	X	X	X	X	X	X	X	X
Diary Scores		X		X[i]	X	X	X	X	X	X	X	X
Concomitant medications		X		X	X	X	X	X	X	X	X	X
Preexisting conditions		X										

Adverse events			X	X	X	X	X	X	X	X

(continued)

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Investigational drug dose modifications				X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]		
Investigational product returned and compliance assessed					X	X	X	X	X	X		
Laboratory												
Hematology		X		X[l]	X	X	X	X	X	X	X	X
Serum chemistry		X		X[l]	X	X	X	X	X	X	X	X
Fasting lipid panel		X					X	X	X	X	X	
Urinalysis		X		X[l]	X	X	X	X	X	X	X	X
HBsAg, HBcAb, HBsAb		X[m]										
Hepatitis C antibody		X[m]										
HIV		X[m]										
Thyroid stimulating hormone		X[f]										
Serum pregnancy test[n]		X										
Urine pregnancy test[n]				X	X	X	X	X	X	X	X	X
Serum baricitinib concentration[o]				X	X	X	X	X	X	X		
Pulmonary function tests (SAVI		X		X	X	X	X	X	X	X	X	

patients only)[p]											

Abbreviations and footnotes on next page.

Abbreviations: ET = early termination; JDM = juvenile dermatomyositis; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibiody; HBsAb = hepatitis B surface antibody; HIV = human immunodeficiency virus; SAVI = STING-associated vasculopathy with onset during infancy.

a Early termination visit is required if early termination occurs.
b Visits occur at approximately 4-week intervals during Weeks 16 through 52 (including both required and optional visits)
c Visits occur at approximately 12-week intervals during Weeks 60 through 288.
d Visit 2 encompasses the initial dosing period and can vary in time depending on whether the patient progresses through the first and second dose escalation during this period. Four days is the minimum time.
e Every effort should be made to schedule patient visits within the allowable visit window; however, if a patient visit is scheduled outside the visit window, it will not be considered a protocol violation.
f If results are available from testing within 1 month, then the patient will not have to be retested.
g If a chest x-ray has not been performed in the 6 months prior to screening visit.
h Juvenile dermatomyositis patients only.
i At least 2 weeks of diary scores are required prior to beginning investigational product.
j Each time study dose is adjusted during Visit 2, this eCRF will be completed.
k See dose escalation schedule (**Table JAGA.7.1**). Each time study dose is adjusted, this eCRF will be completed. Collect samples for chemistry, hematology, and urinalysis 2 weeks after final dose increase. Collect pharmacokinetic samples as described in Section **10.3.2**.
l Collect prior to each dose escalation. Investigator will review to ensure dose escalation is appropriate. Collect prior to the last dose given at Visit 2.
m If results are available from testing within the previous 3 months, then the patient will not have to be retested.
n 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 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
o Baricitinib concentration samples will be collected as described in Section **10.3.2**. Samples will be collected after Visit 2 only if patient has a dose escalation (see **Table JAGA.7.1**).
p Pulmonary function tests are required for SAVI patients only. Pulmonary function tests may include vital signs, pulse oximetry, imaging, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide. During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased.
q These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2.
r Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained locally.

Attachment 2. Protocol I4V-MC-JAGA Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b,c]	**Serum Chemistry**[a,b]
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin[c]
Mean cell volume (MCV)	Direct bilirubin[c]
Mean cell hemoglobin concentration (MCHC)	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT/SGPT)[c]
Reticulocyte	Aspartate aminotransferase (AST/SGOT)[c]
Absolute counts of:	Blood urea nitrogen (BUN)[c]
Neutrophils, segmented	Creatinine[c]
Neutrophils, juvenile (bands)	Calcium
Lymphocytes	Glucose
Monocytes	Albumin
Eosinophils	Total protein
Basophils	Creatine phosphokinase (CPK)
Platelets	Uric acid
Cell Morphology	Gamma glutamyl transferase (GGT)
	Aldolase[d]
Lipid[e]	
Total cholesterol (TC)	
Low-density lipoprotein (LDL)	
High-density lipoprotein (HDL)	**Other Tests**[a]
Triglycerides	Hepatitis B Surface antigen (HBsAg)[g]
	Anti-Hepatitis B Core antibody (HBcAb)[g]
Urinalysis[a,b,f]	Hepatitis B Surface antibody (HBsAb)[g]
Color	Hepatitis B Virus DNA[g]
Specific gravity	Human immunodeficiency virus (HIV)[g]
pH	Hepatitis C antibody[h]
Protein	Thyroid-stimulating hormone (TSH)[g]
Glucose	Thyroxine (T4)[g]
Ketones	Pregnancy Test[i]
Bilirubin	QuantiFERON®-TB Gold[g,j]
Urobilinogen	Baricitinib serum concentration
Blood	
Leukocyte esterase	
Nitrite	

Abbreviations: PPD = purified protein derivative; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis; WBC = white blood cells.

Footnotes on next page.

a Assayed by local clinical laboratory.
b Unscheduled blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator.
c If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2.
d Perform if inflammatory myositis is present.
e Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to test.
f Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.
g Test required at Visit 1 only to determine eligibility of patient for the study.
h A positive hepatitis C antibody result will be confirmed with a positive hepatitis C virus result.
i For all women of childbearing potential, a serum pregnancy test will be performed at Visit 1 and a urine pregnancy test (local laboratory) will be performed at Visit 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
j The QuantiFERON®-TB Gold 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. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

Attachment 3. Protocol I4V-MC-JAGA Sampling Summary

This table summarizes the maximum number of samples and volumes for all sampling and tests during the entire 292-week study period, including the optional visits. The volume of blood drawn is less than the maximum recommended volume in both the National Institutes of Health and World Health Organization guidelines (Howie 2011) for pediatric patients. Fewer samples may actually be taken, but this will not require a protocol amendment.

	All Patients		
	Maximum Volume per Sample	**Maximum Number of Samples**	**Maximum Total Volume**
<30 kg			
Screening laboratory tests	7 mL	1	7 mL
Standard laboratory tests[a]	7 mL	36	252 mL
Drug concentration[b]	1.2 mL	12	14.4 mL
Total volume of blood			**273.4 mL**
30 to <40 kg			
Screening laboratory tests	7 mL	1	7 mL
Standard laboratory tests[a]	7 mL	36	252 mL
Drug concentration[b]	1.2 mL	12	14.4 mL
Total volume of blood			**273.4 mL**
40 to <50 kg			
Screening laboratory tests	7 mL	1	7 mL
Standard laboratory tests[a]	7 mL	37	259 mL
Drug concentration[b]	1.2 mL	18	21.6 mL
Total volume of blood			**287.6 mL**
50 to <60 kg			
Screening laboratory tests	7 mL	1	7 mL
Standard laboratory tests[a]	7 mL	37	259 mL
Drug concentration[b]	1.2 mL	18	21.6 mL
Total volume of blood			**287.6 mL**
>60 kg			
Screening laboratory tests	7 mL	1	7 mL
Standard laboratory tests[a]	7 mL	37	259 mL
Drug concentration[b]	1.2 mL	18	21.6 mL
Total volume of blood			**287.6 mL**

Footnotes on next page.

[a] Standard laboratory tests include chemistry, hematology, and lipid panels.
[b] The protocol allows for additional dose escalations with sponsor consultation and approval. These potential additional dose escalations would require additional drug concentration samples not reflected here.

Attachment 4. Protocol I4V-MC-JAGA Recommended Hepatic Evaluation Guidance Document

Clinical laboratory investigation is highly recommended for diagnosis and monitoring based on the following recommendations adapted from the Drug Induced Liver Injury Guidance published by the FDA in July 2009. Investigators are encouraged to use clinical judgment and may consult with the Lilly clinical research physician for further clarification as necessary.

If an isolated elevation in ALT/AST ≥3 times and ≤5 times ULN or total bilirubin ≥2 times ULN occurs, the patient should be closely observed, including:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the investigational product has been discontinued and the patient is asymptomatic. Monitor AST, ALT, total bilirubin, and alkaline phosphatase until aminotransferase enzymes (ALT, AST) return to <3 times ULN and total bilirubin level <2 times ULN.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases, including history of liver abnormalities or disease (for example, Gilbert's disease) in the patient's family
- Obtaining a history of recent concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtaining a history of exposure to environmental chemical agents (for example, occupational or recreational exposure)
- Obtaining additional tests to evaluate liver function, as appropriate (for example, international normalized ratio, direct bilirubin)
- Consider obtaining gastroenterology or hepatology consultations

In patients with JDM, elevations in ALT/AST up to 5 times ULN may be determined to be myositis-related, subject to the results of additional investigations and clearly stated independent expert opinion, as described in exclusion criterion 31, Section 8.3.2.

If an isolated elevation in ALT/AST >5 times ULN, perform all of the above and obtain gastroenterology or hepatology consultation.

Attachment 5. Protocol I4V-MC-JAGA Patient Diaries

CANDLE and CANDLE - Related Diary

Date of last clinic visit: _____ Study #: 12-AR-8001 / JAGA Subject # _____ Month/Year of this diary page: _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column.

Total Daily Dose _____ (mg)

Dose breakdown _____ (mg)

Dose Frequency - circle or check one. (number of doses per day)	
If your dose or dose frequency changes, start a new diary page starting with the current calendar day.	1 time per day ☐
	2 times per day ☐
	3 times per day ☐
	4 times per day ☐
	5 times per day ☐

					0 = No fever 1 = Fever without impact on daily activity 2 = Fever requiring fever-reducing medication or with mild impact on daily activity 3 = Fever requiring medication with significant impact on daily activities (missing school, fatiguness) 4 = Fever forcing the patient to be bedridden	0 = No rash 1 = Rash barely present 2 = Rash covering 10% of body surface area 3 = Rash covering more than 30% of body surface area 4 = Worst rash ever or covering over 30% of body surface area or hurting or stinging	0 = No pain 1 = Mild pain not requiring medication, no limping 2 = Pain requiring medication or leading to limping or other mild functional impact 3 = Pain requiring medication or having a severe functional impact 4 = Severe pain, child refusing to walk, or staying in bed most of the time	0 = No headache 1 = Mild headache not requiring medication or any adjustments of daily activities 2 = Headache requiring medication or having mild functional impact 3 = Headache requiring medication and having a severe functional impact 4 = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	0 = No fatigue 1 = Mild fatigue, no functional impact 2 = Moderate fatigue with mild functional impact 3 = Severe fatigue with a severe functional impact 4 = Severe fatigue resulting in patient staying in bed most of the time		Who completed the diary today? S = Subject P = Parent M = Medical Staff O = Someone else (do not enter names)
Day	Date MM/DD/YYYY	Total Daily Dose JAGA (mg) Given	Missed JAGA Dose (mg) & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Dose of Steriods (mg)	
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
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28											
29											
30											
31											

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JDM Diary

Date of last clinic visit: _____ Study #: 12-AR-8001 / JAGA Subject # _____ Month/Year of this diary page: _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

Total Daily Dose _____ (mg)

Dose breakdown _____ (mg)

Dose Frequency - circle or check one. (number of doses per day) If your dose or dose frequency changes, start a new diary page starting with the current calendar day.	
1 time per day	☐
2 times per day	☐
3 times per day	☐
4 times per day	☐
5 times per day	☐

					0 = No fever	0 = No rash	0 = No pain	0 = No headache	0 = No fatigue	0 = No muscle		
					1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild headache not requiring medication or any adjustments of daily activities	1 = Mild fatigue, no functional impact	1 = Mild weakness		
					2 = Fever requiring fever-reducing medication or with mild impact on daily activity	2 = Rash generally brighter pink to red	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Headache requiring medication or having mild functional impact	2 = Moderate fatigue with mild functional impact	2 = Moderate weakness		
					3 = Fever requiring medication with significant impact on daily activities (missing school, listlessness)	3 = Rash generally bright red	3 = Pain requiring medication or having a severe functional impact	3 = Headache requiring medication and having a severe functional impact	3 = Severe fatigue with a severe functional impact	3 = Severe weakness		
					4 = Fever forcing the patient to be bedridden	4 = Worst rash ever	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	4 = Severe fatigue resulting in patient staying in bed most of the time	4 = Extremely severe weakness		
Day	Date MM/DD/YYYY	Total Daily Dose JAGA mg Given	Missed JAGA Dose & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Weakness	Dose of Steriods (mg)	Who completed the diary today? S = Subject P = Parent M = Medical Staff O = Someone else (do not enter names)
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
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27												
28												
29												
30												
31												

Key for scoring per symptom:

Fever	0 - 4 listed above
Rash	0 = no rash
	1 = Faint pink - involvement of a smaller area, such as joints, eyelids, and/or cheeks
	2 = Pink to red - involvement of moderate area, such as joints, face, hands, and arms, neck, and/or shoulders
	3 = Bright red - often with more extensive involvement of moderate area, such as joints, face, neck & shoulders, hands & arms, lower extremities, & possibly trunk or buttocks
	4 = Worst - Extremely bright red & often with itchiness, scratching, or with secondary changes of blisters, scabs
Musculoskeletal	0 - 4 listed above
Headache	0 - 4 listed above
Fatigue	0 - 4 listed above
Weakness	0 = No weakness - Strong in all muscle groups & have no problems with their muscle strength or ability to do things compared to their peers
	1 = Mild Weakness - Almost normal strength in all muscles & can do almost everything with their muscles that their peers can do with minimal/mild problems
	2 = Moderate Weakness - Their muscles are somewhat weak; can do things with their muscles, but using their muscles for many things is hard for them)
	3 = Severe Weakness - Their muscles are very weak & using their muscles for most things is hard for them; they need assistance with some things)
	4 = Extremely Severe Weakness - Their muscles are extremely weak & using their muscles for everything is hard for

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SAVI Diary

Date of last clinic visit: _____ **Study # 12-AR-8001 / JAGA** **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

Total Daily Dose _____ **(mg)**

Dose breakdown _____ **(mg)**

Dose Frequency – circle or check one. (number of doses per day)
If your dose or dose frequency changes, start a new diary page starting with the current calendar day.

- 1 time per day ☐
- 2 times per day ☐
- 3 times per day ☐
- 4 times per day ☐
- 5 times per day ☐

	0 = No fever	0 = No rash	0 = No pain	0 = No fatigue	0 = No breathing problems	0 = No ulcers
	1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild fatigue, no functional impact	1 = Mild breathing problems / rapid breathing / coughing, no functional impact	1 = Few ulcers, only in 1 location and/or no drainage, no ischemia
	2 = Fever requiring fever-reducing medication or with mild impact on daily activity	2 = Rash covering 10% of body surface area	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Moderate fatigue with mild functional impact	2 = Moderate breathing problems / rapid breathing / coughing with mild functional impact	2 = Ulcers in more than 1 location and/or with some drainage, no ischemia
	3 = Fever requiring medication with significant impact on daily activities (missing school, intolerance)	3 = Rash covering more than 30% of body surface area	3 = Pain requiring medication or having a severe functional impact	3 = Severe fatigue with a severe functional impact	3 = Severe breathing problems / rapid breathing / coughing with a severe functional impact	3 = Ulcers in multiple locations and/or significant drainage, and/or any ischemia
	4 = Fever forcing the patient to be bedridden	4 = Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe fatigue resulting in patient staying in bed most of the time	4 = Severe breathing problems / rapid breathing / coughing which result in patient staying in bed most of the time	4 = Severe ulcers / ischemic lesions in multiple locations

Day	Date MM/DD/YYYY	Total Daily JAGA Dose Given (mg)	Missed JAGA Dose & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Fatigue	Respiratory/ Breathing Symptoms	Ulcers / Ischemic lesions	Dose of Steriods (mg)	Peak Flows	Who completed the diary today? S = Subject P = Parent M = Medical Staff O = Someone else (do not enter names)
1													
2													
3													
4													
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Attachment 6. Protocol I4V-MC-JAGA Bohan and Peter Criteria for the Diagnosis of Polymyositis and Dermatomyositis

Criteria for the Diagnosis of Polymyositis and Dermatomyositis[a]

Criterion	Definition
1. Symmetrical Weakness	Weakness of limb-girdle muscles and anterior neck flexors progressing over weeks to months with or without dysphagia or respiratory muscle involvement
2. Muscle Biopsy Evidence	Evidence of necrosis of Type I and II fibers, phagocytosis, regeneration with basophilia, large vesicular sarcolemmal nuclei and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size, and an inflammatory exudate, often perivascular
3. Elevation of Muscle Enzymes	Elevation in serum of skeletal muscle enzymes, particularly creatine phosphokinase and often aldolase, serum glutamate oxaloacetate, pyruvate transaminases, and lactate dehydrogenase
4. Electromyographic Evidence	Electromyographic triad of short, small, polyphasic, motor units, fibrillations, positive sharp waves, and insertional irritability, and bizarre, high-frequency, repetitive discharges
5. Dermatologic Features	A lilac discoloration of the eyelids (heliotrope) with periorbital edema, a scaly erthematous dermatitis over the dorsum of the hands (especially the metacarpophalangeal and proximal interphalangeal joints, Gottron's sign), and involvement of the knees, elbows, and medial malleoli, as well as the face, neck, and upper torso

[a] Confidence limits can be defined as follows: For a definite diagnosis of dermatomyositis, 3 of 4 criteria plus the rash must be present. For a probable diagnosis of dermatomyositis, 2 criteria plus the rash must be present. For a possible diagnosis of dermatomyositis, 1 criterion plus the rash must be present.

Data from Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med.* 1975;292(7):344–347, with permission.

Attachment 7. Protocol I4V-MC-JAGA Juvenile Dermatomyositis Core Set Measures

Core Set Measures

Domain	Core Set Measures
Global Activity	Physician global disease activity assessment by Likert or VAS Parent/patient global disease activity assessment by Likert or VAS
Muscle Strength	MMT by a 0 to 10 point or expanded 0 to 5 point scale to include proximal, distal, and axial muscles (adults and children ≥4 years of age)
Physical Function	Validated parent/patient questionnaire of activities of daily living (HAQ/CHAQ)
Laboratory Assessment	Activity of at least one serum muscle enzyme from the following: creatine kinase (CK), aldolase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)
Extramuscular Disease	A validated approach that is comprehensive and assesses cutaneous, gastrointestinal, articular, cardiac, and pulmonary activity. Myositis Disease Activity Assessment Tool has been validated.

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; HAQ = Health Assessment Questionnaire; MMT = Manual Muscle Test – 8 designated muscles; VAS = visual analog scale.

Manual Muscle Testing – 8 Designated Muscles

Muscle Groups	Right (0 – 10)	Left (0 – 10)	Axial (0 – 10)
Axial Muscles (0 – 10)			
Neck Flexors	—	—	0 – 10
Proximal Muscles (0 – 100)			
Deltoid	0 – 10	0 – 10	—
Biceps brachii	0 – 10	0 – 10	—
Gluteus maximus	0 – 10	0 – 10	—
Gluteus medius	0 – 10	0 – 10	—
Quadriceps	0 – 10	0 – 10	—
Distal Muscles (0 – 40)			
Wrist extensors	0 – 10	0 – 10	—
Ankle dorsiflexors	0 – 10	0 – 10	—
MMT-8 Score (0 – 150)	0 – 70	0 – 70	0 – 10

Abbreviations: MMT = Manual Muscle Test – 8 designated muscles.

Attachment 8. Protocol I4V-MC-JAGA Myositis Patient/Parent Global Activity Assessment

IMACS FORM 03: PATIENT/PARENT GLOBAL ACTIVITY ASSESSMENT

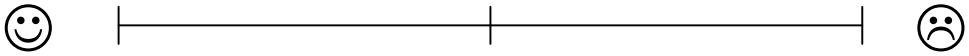
Assessor _____

Assessor's relationship to subject: Patient__; Mother:__; Father__; Other (specify):_____

Date of assessment (mm/dd/yy) _____

Your myositis is the result of the combined effects of many disease processes. One of these is disease activity, which is active inflammation in your/your child's muscles, skin, joints, intestines, heart, lungs or other parts of your body, which can improve when treated with medicines.

1. Considering all the ways that myositis affects you/your child, please rate the overall activity of your/your child's disease today by placing a mark on the line below.



No evidence of disease activity

Extremely active or severe disease activity

Attachment 9. Protocol I4V-MC-JAGA Myositis Physician's Global Activity Assessment

IMACS FORM 02: PHYSICIAN GLOBAL ACTIVITY ASSESSMENT

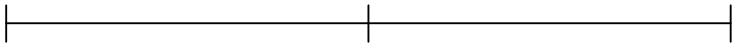
Assessor _____

Date of assessment (mm/dd/yy) _____

Physician Global Activity Assessment

Disease Activity is defined as potentially reversible pathology or physiology resulting from the myositis. Clinical findings known or suspected to be due to another disease process should not be considered in this evaluation. The global assessment of disease activity is to be judged from all the information available to you today including the subject's appearance, history, physical examination, diagnostic laboratory testing and your resultant medical therapy.

Please rate your global (overall) disease activity assessment by drawing a vertical mark on the 10-cm. line below according to the following scale: left end of line = no evidence of disease activity, midpoint of line = moderate disease activity, and right end of line = extremely active or severe disease activity.



No evidence of disease activity — Extremely active or severe disease activity

Also rate global disease activity on a 5-point Likert scale:

___0 = none
___1 = mild activity
___2 = moderate activity
___3 = severe activity
___4 = extremely severe activity

Attachment 10. Protocol I4V-MC-JAGA Myositis Disease Activity Assessment Tool

IMACS FORM 07a: Modified MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL – 2005, Version 2

ASSESSOR:_____ Date Assessed:_____

General Guidelines for Completion:

Please rate your overall (global) assessment of the ongoing **extramuscular** disease activity over the past 4 weeks on the 0-10cm VAS scale by drawing a **vertical** mark on the 10cm line according to the following guidelines:

- left end of line = no evidence of disease activity
- midpoint of line = moderate disease activity
- right end of line = extreme or maximum disease activity

* Clinical findings known or suspected to be due to another disease process or due to therapy should **NOT** be considered in this evaluation
* Disease activity is defined as a potentially reversible finding.
* Myositis or muscle disease activity should be excluded from this assessment.

Extramuscular Global Assessment	**(Absent)** **(Maximum)** __ __ . __ cm	Overall evaluation for disease activity in all extramuscular systems **(EXCLUDING MUSCLE DISEASE ACTIVITY)**

Attachment 11. Protocol Amendment I4V-MC-JAGA(r) Summary

Overview

Protocol I4V-MC-JAGA has been amended. The new protocol is indicated by amendment (r) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Extended the duration of the study to 292 weeks to allow for additional treatment time (288 weeks) for participating patients.
- In order to be consistent with an increased understanding of response to baricitinib treatment in these populations, the dose escalation plan has been unified for all patients, regardless of disease, and the <20 kg and 20 to <30 kg dosing group have been combined to form the <30 kg dosing group. The PK section was updated accordingly and sample collection times and PK analyses were clarified.
- Guidance for interruption and discontinuation of investigational product were modified to allow for increased flexibility given the severity of the disease and lack of other treatment options, as well as an increased understanding of response to baricitinib treatment in these populations.
- Given the increased experience with baricitinib treatment in these populations, non-essential visits during the first year of the study have been made optional; and the option to perform some required visits as telephone visits with local labs was added. The summary of study design, study design diagram, and study schedule of events were updated accordingly.
- Added provision for patients who do not meet the inclusion/exclusion criteria to be considered for enrollment upon consultation with the Sponsor due to the severity of the disease and lack of other treatment options.
- Based on clinical experience with patients with CANDLE-related conditions, insterstitial lung disease was added as an indicator of organ specific inflammation in inclusion criterion 46.
- Exclusion criteria 13 and 15 were modified to allow for entry of patients with herpes simplex virus infection or other mild infections that the investigator does not consider an unacceptable risk for participating in the study.
- To increase the convenience of dosing, the 2 mg dose option was added.
- Based on clinical experience with these patients, ECGs will no longer be required after screening and pertinent sections were updated accordingly.
- The patient diaries have been updated to include additional documentation fields.
- Other minor typographical corrections and editorial clarifications not affecting content have been made in the document.

Revised Protocol Sections

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

Section 1. Title Page

Study I4V-MC-JAGA is an open-label compassionate use treatment program to provide baricitinib to patients with conditions expected to benefit from JAK inhibition: CANDLE, CANDLE-related conditions, SAVI, and severe juvenile dermatomyositis. Patients will receive an initial dose based on their weight class and disease type that may be escalated to determine a tolerable dose. Patients may be dosed for up to ~~260~~ 288 weeks. It is anticipated that up to 35 patients may be treated with baricitinib in an individualized manner. The treatment guidelines contained herein are for compassionate use only. Within these guidelines, open-label baricitinib will only be administered to patients who meet inclusion and exclusion criteria.

Section 2. Synopsis

Length of Study: Up to ~~264~~292 weeks

Study Design: An open-label, compassionate use treatment protocol. Patients will be treated for a maximum of ~~260~~288 weeks.

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder for which there is reason to believe that JAK 1/2 inhibition will be beneficial. One such autoinflammatory disorder is chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. CANDLE syndrome 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). Other patients eligible to be enrolled into this study include those diagnosed with conditions related to CANDLE syndrome involving immune dysregulation: stimulator of interferon genes (STING)-associated ~~vasculitis~~vasculopathy with onset in infancy (SAVI), an autoinflammatory syndrome with interferon (IFN) pathway dysregulation, and juvenile dermatomyositis (JDM).

Planned Duration of Treatment: Each patient may be treated up to ~~260~~288 weeks.

Section 4. Abbreviations and Definitions

~~**AESI**~~	~~adverse events of special interest~~
~~BID~~	~~twice daily~~
~~case report form (CRF) and electronic case report form (eCRF)~~	~~Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.~~

~~CHAQ~~	~~Childhood Health Assessment Questionnaire~~
~~CIOMS~~	~~Council for International Organizations of Medical Sciences~~
~~CNS~~	~~central nervous system~~
~~DIRA~~	~~deficiency of IL-1 receptor antagonist~~
~~DLCO~~	~~diffusing capacity of the lung for carbon monoxide~~
Electronic case report form (eCRF)	Sometimes referred to as clinical report form. A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
~~ESRD~~	~~end-stage renal disease~~
~~FMF~~	~~familial Mediterranean fever~~
~~GGT~~	~~gamma-glutamyl transferase~~
~~GM-CSF~~	~~granulocyte macrophage colony-stimulating factor~~
~~HAQ~~	~~Health Assessment Questionnaire~~
~~HBcAb~~HBV	hepatitis B ~~core antibody~~virus
~~HBsAb~~	~~hepatitis B surface antibody~~
~~HBsAg~~	~~hepatitis B surface antigen~~
~~HCV~~HIV	~~hepatitis C~~human immunodeficiency virus
~~HDL~~i-proteasome	~~high-density lipoprotein~~immunoproteasome complex
~~HIDS~~IC50	~~hyperimmunoglobulin D with periodic fever syndrome~~half maximal inhibitory concentration
~~IB~~	~~Investigator's Brochure~~
IC50	half maximal inhibitory concentration
~~ICH~~	~~International Conference on Harmonisation~~
IFN	interferon
IL	interleukin
IP-10/CXCL10	interferon inducible protein 10/ C-X-C motif chemokine 10
~~IPA~~	~~Ingenuity Pathway Analysis~~
~~IV~~	~~intravenous~~
JAGA	I4V-MC-JAGA

~~LDL~~	~~low-density lipoprotein~~
~~MDAAT~~	~~Myositis Disease Activity Assessment Tool~~
~~MMT~~	~~Manual Muscle Testing~~
~~MVK~~	~~mevalonate kinase~~
~~NIH~~	~~National Institutes of Health~~
PK~~/PD~~	pharmacokinetics~~/pharmacodynamics~~
~~PRO~~	~~patient-reported outcome~~
~~QTc~~	~~corrected QT interval~~
~~RBC~~	~~red blood cell~~
SAVI	STING-associated ~~vaseulitis~~ vasculopathy with onset during infancy
~~T4~~	~~thyroxine~~
~~TRAPS~~	~~TNF receptor-associated periodic syndrome~~
~~TSH~~	~~thyroid-stimulating hormone~~
~~WHO~~	~~World Health Organization~~

Section 5. Introduction

Representative JAK/STAT-dependent cytokines involved in the inflammation associated with innate and adaptive immunity include type I and II interferons (IFNs), interleukin (IL)-2, IL-6, IL-12, IL-23, and granulocyte macrophage colony-stimulating factor ~~(GM-CSF).~~.

Baricitinib is being investigated for the treatment of inflammatory diseases, including RA and Ps. 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 single 5-mg doses to subjects with end stage renal disease ~~(ESRD).~~.

* CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature

SAVI = stimulator of interferon genes (STING)-associated ~~vaseulitis~~vasculopathy with onset during infancy

The most common alterations in laboratory values involve decreases in hemoglobin, hematocrit, total red blood cells ~~(RBCs),~~ and white blood cells ~~([~~[WBCs~~;]~~; neutrophils and other white cell lines), and increases in platelet counts, high-density lipoprotein ~~(HDL),~~ low-density lipoprotein ~~(LDL),~~ 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 ~~(IB).~~. Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the ~~IB~~Investigator's Brochure.

Most of these diseases include fever, urticaria-like rash, and arthralgia, and are associated with gain of function mutations in the inflammasome, including, but not limited to, mutations in the ~~NRLP3~~ NLRP3 gene (McGonagle et al. 2006).

To this extent, loss of function mutations in the proteasome subunit beta type-8 (PSMB8) gene encoding the beta5i 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 gamma IFN, IL-6, and IL-2 receptor (Agarwal et al. 2010).

- ~~**SAVI (STING-Associated Vasculitis with onset during Infancy).**~~**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 ~~vasculitis~~vasculopathy and interstitial lung disease (~~R Goldbach-Mansky, personal communication, 2013).~~Liu et al. 2014). Four other unrelated children (total of 5 children) with similar clinical phenotypes described have been identified to have mutations in the same gene using targeted sequencing of the candidate gene (~~R Goldbach-Mansky, personal communication, 2013~~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. Another patient harbors a *de novo* mutation at position c.442G>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 wildtype. 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 tumor necrosis factor (TNF). The clinical phenotype and the increased IFN response gene expression in the peripheral blood suggest a gain of function resulting in a severe autoinflammatory phenotype with interstitial lung disease progressing to interstitial fibrosis with focal emphysema and acral ~~vasculitis~~vasculopathy, resulting in necrosis and loss of fingers/toes, ulcerating skin lesions, fevers, and elevated inflammatory markers. This condition is described as SAVI (~~STING-associated vasculitis with onset during infancy~~Liu et al. 2014).

- **CANDLE-Related Conditions.** A group of conditions that have very strong IFN~~interferon~~ response signature have recently been identified in the gene expression studies from whole blood. These conditions share clinical, pathological, and immunological features, which are different from those typically observed in IL-1-mediated autoinflammatory diseases (including NOMID, ~~DIRA, HIDS, TRAPS~~deficiency of IL-1 receptor antagonist, hyperimmunoglobulin D with periodic fever syndrome, TNF receptor-associated periodic syndrome, and ~~FMF~~familial Mediterranean fever) that respond to IL-1 inhibition. Many of the ~~interferon~~IFN-associated conditions do not respond to IL-1 blockade and share a clinical phenotype that may include vasculopathy (hypertension, vascular calcifications such as basal ganglia calcifications, or livedo reticularis), metabolic changes (lipodystrophy, dyslipidemia, insulin resistance, or intra-abdominal fat deposition), myositis, arthralgias or arthritis, and/or panniculitis. In these conditions, histologic features of immature neutrophils in the inflammatory infiltrate are commonly seen on skin biopsy.

Conditions of Immune Dysregulation – Juvenile Dermatomyositis

~~Juvenile dermatomyositis (JDM)~~JDM is traditionally viewed as an autoimmune (adaptive immune) disease. Characteristic clinical signs and symptoms include fatigue, fever, symmetrical weakness of the proximal musculature, and characteristic cutaneous changes consisting of heliotrope discoloration of the eyelids, which may be accompanied by periorbital edema and erythematous papules over the extensor surfaces of joints (Gottron papules). ~~Juvenile dermatomyositis~~JDM may also be associated with panniculitis-induced lipodystrophy and metabolic abnormalities, such as hyperlipidemia. Support for a diagnosis of JDM is provided by elevated serum levels of muscle enzymes and the histopathological observation of inflammatory myositis on muscle biopsy. Peripheral blood cells show a characteristic pattern of high expression of IFN regulated genes (known as an IFN signature).

~~Juvenile dermatomyositis~~JDM is the most common form of idiopathic inflammatory myopathy in children, with an average age of onset of 7 years.

Myositis-associated and -specific autoantibodies have been seen in approximately 40% of JDM patients (Khanna and Reed 2010) and vascular injury with endothelial dysfunction, complement activation, and antibody deposition on small vessels is also apparent and associated with disease progression. Consistent with the contribution of both innate and adaptive immunity to the disease process, increases in circulating IL-6 and type 1 IFN-induced chemokines, including ~~CXCL10 and MCP~~IFN inducible protein 10/ C-X-C motif chemokine 10 (IP-10/CXCL10) and monocyte chemoattractant protein-1, have been reported in JDM patients (Bilgic et al. 2009; Greenberg 2010). Furthermore, these circulating biomarkers are correlated with global visual analog scale (VAS) scores (Bilgic et al. 2009). ~~Interleukin~~IL-6 and Type 1 IFNs signal through the JAK-STAT pathway, supporting a hypothesis that inhibition of this pathway could provide a viable therapeutic option.

Summary

In Study I4V-MC-JAGA~~,~~ (JAGA), a within-patient dose-escalation treatment regimen of baricitinib will be utilized.

Section 5.1.1. The Role of IL-1 in Autoinflammatory Diseases

The clinical and basic research unraveling of the CIAS1/NLRP3 inflammasome, a crucial platform to activate IL-1β and controlling its release, has revealed a key inflammatory pathway that is not only constitutively activated in CAPS, but also is activated through cellular "danger molecules," including uric-acid crystals in gout (Dalbeth and So 2010), ceramide, oxidized ~~LDL~~low-density lipoprotein, and glucose in type 2 diabetes mellitus (De Nardo 2011), and cholesterol crystals in coronary artery disease (Goldbach-Mansky 2009; Duewell 2010).

Section 5.2 CANDLE Syndrome and Related Non-IL-1 Dependent Autoinflammatory Diseases

An autoinflammatory disorder has recently been characterized that does not respond to treatment with IL-1, TNF, and only partially to IL-6-blocking agents ~~(R Goldbach-Mansky, personal communication, 2013)~~ (Liu et al. 2012).

~~Although~~ CANDLE patients have some overlapping features with JMP patients, including a cutaneous eruption and lipodystrophy (Garg et al. 2010~~), none of~~). Although the patients ~~studied has developed~~ reported as JMP had more prominent joint contractures and muscle atrophy~~, 2 prominent symptoms featured in JMP. CANDLE~~ than patients~~, on the other hand, showed several key features that have not been~~ described ~~in~~as CANDLE, the difference may be due to a reporting bias. Nevertheless, the ~~JMP~~detection of the same and additional mutations in PSMB8 unifies these disorders as an i-proteasome associated autoinflammatory syndrome. CANDLE patients~~, particularly~~ 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 syndrome. In fact, 2 patients have been misdiagnosed with acute cutaneous myelogenous leukemia. ~~The difference may partly be due to a reporting bias. Nevertheless, the detection of the same and additional mutations in PSMB8 unifies these disorders as an i-proteasome associated autoinflammatory syndrome.~~

Section 5.3 Functional Data Supporting a Rationale to Block IFN Signaling

As mentioned above, empiric treatment with targeted agents to TNF, IL-1, and IL-6 have been unsuccessful. 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 (~~IP-10~~) (~~/CXCL10~~)~~ serum levels, were on average over 77-fold higher than controls. The very high levels of IP-10/CXCL10 suggested excessive IFN responses in CANDLE patients.

Differentially expressed genes (DEGs) were analyzed by the Ingenuity Pathway Analysis ~~(IPA)~~ program to identify dysregulated canonical pathways, and the IFN pathway was the most differentially regulated in CANDLE patients ($p=4.73^{E-06}$).

Although temporary clinical improvement was seen with anti-TNF-alpha and anti-IL-6 treatment (~~R Goldbach-Mansky, personal communication, 2011~~Liu et al. 2012), the "IFN signature" did not improve.

Interestingly, in an active SAVI patient, STAT-1 and STAT-5 were maximally phosphorylated and could not have been further activated (~~R Goldbach-Mansky, personal communication, 2013).~~Liu et al. 2014, supplementary materials). Preliminary data using tofacitinib in cells of SAVI patients suggest that the IFN response genes can be downregulated when blocking with tofacitinib (~~R Goldbach-Mansky, personal communication, 2013~~Liu et al. 2014) supporting the hypothesis that patients with SAVI may respond to JAK1/JAK2 inhibition.

Section 5.4 In Vitro Data on Loss of I-Proteasome Function in *Psmb8/Lmp7* Knockout Mice

26S proteasomes are multi-subunit protein complexes critical for degradation of polyubiquitynated proteins within cells. The 20S core complex consists of 2 alpha rings and 2 beta rings, each having 7 different alpha (α) or beta (β) subunits. ~~Immunoproteasomes (~~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 ~~MHC~~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).

There is evidence that the patients' cells have accumulated polyubiquitynated proteins, an indication of decreased proteasome activity (~~R Goldbach-Mansky, personal communication,~~Arima et al. 2011).

Section 5.5. In Vitro Evidence for Using a JAK Inhibitor

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).

Section 7.1 Summary of Study Design

Any physical complaints/symptoms that present prior to initiation of treatment with baricitinib will be collected as preexisting conditions on the electronic case report form (~~CRF~~eCRF). Signs and symptoms collected on the patient diary need not be reported as a preexisting condition/~~adverse event~~AE on the ~~CRF~~eCRF unless the signs and symptoms are considered strictly drug related or associated with an outcome defining a serious adverse event (SAE). Current use of concomitant medications and reasons for use will also be collected on the ~~CRF~~eCRF.

Baricitinib will be dosed by patient weight range ~~and disease type.~~. See Table JAGA.7.1 for the dosing schedule ~~for CANDLE patients and Table JAGA.14.2 for non-CANDLE (CANDLE-related condition, SAVI, and JDM) patients. CANDLE~~. All patients will receive an initial twice-daily dose; patients ~~in the upper weight classes~~ may have their dose escalated. Patients must receive a dose for at least ~~3 days before a dose escalation can occur. Non-CANDLE patients will receive an initial once-daily dose that may be escalated; dose escalation will add an evening dose to the established morning dose. Patients must receive a dose for at least 3 days~~72 hours before a dose escalation can occur.

Every effort should be made to follow the dose escalation schedule shown in Table JAGA.7.1 ~~or Table JAGA.14.2.~~. However, if a patient's condition warrants an accelerated dose escalation schedule, this may be allowed after consultation with the Sponsor. Additionally, in the event of adverse events 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 data. Where possible, these decisions should be taken following documented agreement between the investigator and sponsor; however, in emergency situations the investigator may take these actions. In such situations, the sponsor should be informed as soon as possible. Any subsequent dose restarts or increments will occur only after review of clinical data and documented agreement between the investigator and sponsor.

Pharmacokinetic ~~(PK)~~ Sampling

Samples will be collected when the patient reaches steady state at the target dose level after approximately ~~3 days~~72 hours of treatment.

Continuing Treatment

~~Adverse events~~AEs and concomitant medications will be assessed over the phone or in person by the study team. Once the patient has reached a stable dose of baricitinib, the same total dose may be administered as equal or unequal divided doses (administered up to 4 doses in a day~~).~~ [24 hours]). If more than 4 doses are needed in 1 day~~,~~ (24 hours), then consultation and agreement with the Sponsor will be required.

2. If a patient remains unresponsive to the ~~initial~~ baricitinib dose, the dose should be increased in the dose escalation steps shown in Table JAGA.7.1 ~~or Table JAGA.14.2.~~. Patients must have received a dose for at least ~~3 days~~72 hours before continuing to the next dose increase. ~~For non-CANDLE patients, prior to beginning dose escalation, the daily dose of baricitinib should be consolidated to 1 morning dose for those patients in whom their dose has been previously divided (for example, 2 mg AM and 1 mg PM will be consolidated to 3 mg AM prior to initiation of dose escalation). The dose increases allowed in Table JAGA.14.2 should be administered as an evening dose.~~ Every effort should be made to follow the dose escalation schedule shown in Table JAGA.7.1 ~~or Table JAGA.14.2.~~.

3. If a patient reaches the maximum allowable dose (Table JAGA.7.1 ~~or Table JAGA.14.2~~) and has an inadequate response to treatment, the patient may be discontinued from the study to pursue other treatment options, or one or both of the following may be considered after consultation with the Sponsor:

(1) The total daily dose may be administered as multiple equal or unequal divided doses.

(2) The patient's dose may be increased above the maximum dose shown in Table JAGA.7.1 ~~or Table JAGA.14.2~~ if, in the opinion of the investigator, this dose increase is warranted based on the clinical assessment of the patient, evaluation of available pharmacokinetic data, and evaluation of renal function. The Sponsor must be consulted before the dose is increased in excess of the maximum dose shown in the dosing tables. For each affected study patient, the conclusion of this consultation must be documented in a way that confirms consensus between the investigator and the Sponsor.

Follow-up appointments will continue during the treatment period according to the Study Schedule (Attachment 1). ~~At all visits, each~~Each patient's ~~use of~~ concomitant medications ~~and~~, investigational product compliance ~~will be reviewed, and~~ , height, weight, ~~and~~ vital signs, and adverse events will be ~~measured. Routine~~assessed; and routine chemistry, hematology, and urinalysis assessments will be performed according to the Study Schedule (Attachment 1). A physical exam will be conducted when the patient completes or discontinues from the study.

As the conditions being treated in this compassionate use program are rare ~~and this protocol is being conducted at a single site~~, patients may be enrolled who must travel a considerable distance to the investigative site. ~~Once patients achieve a stable dose, telephone~~ For most of the required visits ~~will be permissible with collection of height, weight, and vital signs and laboratory testing performed locally. Patients~~ patients should be seen in-person at the investigative site ~~at least every 3 months during the first year of the study and every 6 months during the second through fifth years. The remaining~~. Once patients achieve a stable dose, some required visits my be performed as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally. Optional visits may be performed ~~via telephone~~ at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed.

Baricitinib will be provided to an individual patient for up to ~~260~~288 weeks.

Table JAGA.14.1. Dose Escalation Schedule – CANDLE Patients

Starting Dose				
	Total Daily Dose[b]			
Weight Class[a]	Morning Dose	Evening Dose	Total Dose	Duration[c]
<20 kg	2 mg	2 mg	4 mg	—
20 to <30 kg	3 mg	2 mg	5 mg	3 days
30 to <40 kg	4 mg	2 mg	6 mg	3 days
40 to <50 kg	5 mg	2 mg	7 mg	3 days
50 to <60 kg	6 mg	3 mg	9 mg	3 days
≥60 kg	7 mg	3 mg	10 mg	3 days

First Dose Escalation					
	Evening Dose	Total Daily Dose[b]			
Weight Class[a]	Increase	Morning Dose	Evening Dose	Total Dose	Duration[c]
<20 kg	—	—	—	4 mg	—
20 to <30 kg	+1 mg	3 mg	3 mg	6 mg	—
30 to <40 kg	+2 mg	4 mg	4 mg	8 mg	—
40 to <50 kg	+2 mg	5 mg	4 mg	9 mg	3 days
50 to <60 kg	+2 mg	6 mg	5 mg	11 mg	3 days
≥60 kg	+2 mg	7 mg	5 mg	12 mg	3 days

Second Dose Escalation					
	Evening Dose	Total Daily Dose[b]			Max/Min Dose
Weight Class[a]	Increase	Morning Dose	Evening Dose	Total Dose	(mg/kg)[d]
<20 kg	—	—	—	4 mg	NA/0.2
20 to <30 kg	—	—	—	6 mg	0.30/0.2
30 to <40 kg	—	—	—	8 mg	0.26/0.2
40 to <50 kg	+1 mg	5 mg	5 mg	10 mg	0.25/0.2
50 to <60 kg	+1 mg	6 mg	6 mg	12 mg	0.24/0.2
≥60 kg	+2 mg	7 mg	7 mg	14 mg	0.23/NA

Table JAGA.14.2. Dose Escalation Schedule – Non-CANDLE Patients

Starting Dose		
Weight Class[a]	Starting Dose (Morning)[b]	Duration[b]
<20 kg	2 mg	3 days
20 to <30 kg	3 mg	3 days
30 to <40 kg	4 mg	3 days
40 to <50 kg	5 mg	3 days

~~50 to <60 kg~~	~~6 mg~~	~~3 days~~
~~≥60 kg~~	~~7 mg~~	~~3 days~~

~~**First Dose Escalation[c]**~~

	~~Evening Dose~~	~~Total Daily Dose[b]~~			
~~Weight Class[a]~~	~~Increase~~	~~Morning Dose~~	~~Evening Dose~~	~~Total Dose~~	~~Duration[b]~~
~~<20 kg~~	~~+2 mg~~	~~2 mg~~	~~2 mg~~	~~4 mg~~	~~—~~
~~20 to <30 kg~~	~~+2 mg~~	~~3 mg~~	~~2 mg~~	~~5 mg~~	~~3 days~~
~~30 to <40 kg~~	~~+2 mg~~	~~4 mg~~	~~2 mg~~	~~6 mg~~	~~3 days~~
~~40 to <50 kg~~	~~+2 mg~~	~~5 mg~~	~~2 mg~~	~~7 mg~~	~~3 days~~
~~50 to <60 kg~~	~~+3 mg~~	~~6 mg~~	~~3 mg~~	~~9 mg~~	~~3 days~~
~~≥60 kg~~	~~+3 mg~~	~~7 mg~~	~~3 mg~~	~~10 mg~~	~~3 days~~

~~**Second Dose Escalation**~~

	~~Evening Dose~~	~~Total Daily Dose[b]~~			~~Max/Min Dose~~
~~Weight Class[a]~~	~~Increase~~	~~Morning Dose~~	~~Evening Dose~~	~~Total Dose~~	~~(mg/kg)[e]~~
~~<20 kg~~	~~—~~	~~2 mg~~	~~2 mg~~	~~4 mg~~	~~NA/0.2~~
~~20 to <30 kg~~	~~+1 mg~~	~~3 mg~~	~~3 mg~~	~~6 mg~~	~~0.30/0.2~~
~~30 to <40 kg~~	~~+2 mg~~	~~4 mg~~	~~4 mg~~	~~8 mg~~	~~0.26/0.2~~
~~40 to <50 kg~~	~~+3 mg~~	~~5 mg~~	~~5 mg~~	~~10 mg~~	~~0.25/0.2~~
~~50 to <60 kg~~	~~+3 mg~~	~~6 mg~~	~~6 mg~~	~~12 mg~~	~~0.24/0.2~~
~~≥60 kg~~	~~+4 mg~~	~~7 mg~~	~~7 mg~~	~~14 mg~~	~~0.23/NA~~

~~Abbreviations: max = maximum; min = minimum; NA = not applicable.~~

~~— indicates no further dose escalation allowed.~~

~~[a] See Section 9.4 if a change in the patient's weight during the study would place the patient in a different weight range.~~

~~[b] After reaching a stable dose, the total daily dose can be administered in up to 4 divided doses.~~

~~[c] Duration of treatment prior to escalation includes days to obtain samples and results from safety blood test assessments prior to the first dose or first dose increase.~~

~~[d] Prior to initiation of the first dose escalation, the daily dose will be consolidated to one morning dose for those patients in whom their morning dose has been previously divided.~~

~~[e] Dose in mg/kg for the lowest weight and highest weight in each weight class.~~

Table JAGA.14.3. Dose Escalation Schedule

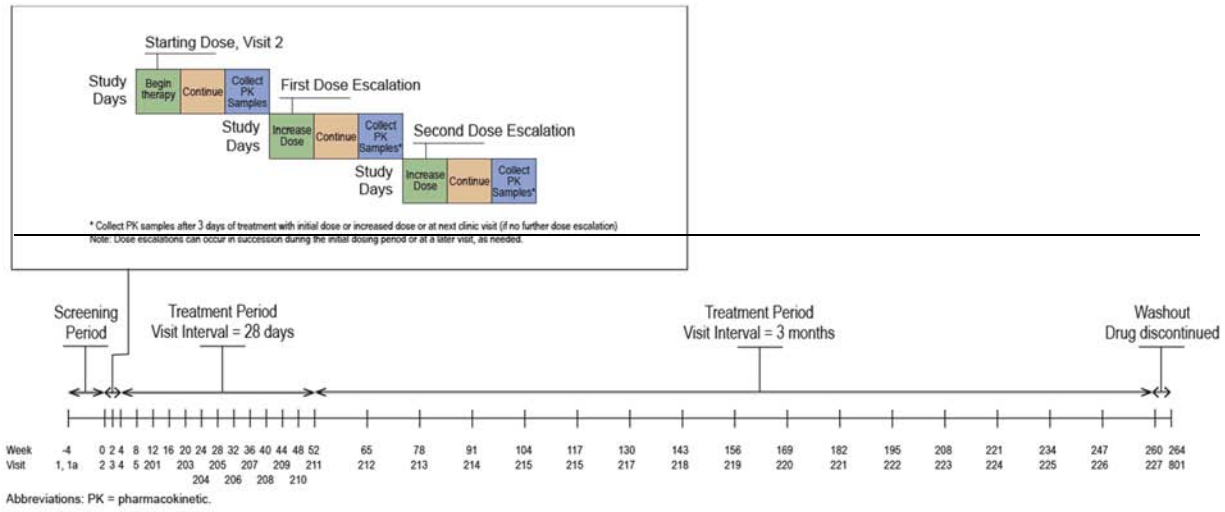
	Starting Dose				
Weight Class[a]	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]
<30 kg	2 mg		2 mg	4 mg	72 hours
30 to <40 kg	4 mg		2 mg	6 mg	72 hours
40 to <50 kg	5 mg		2 mg	7 mg	72 hours
50 to <60 kg	6 mg		3 mg	9 mg	72 hours
≥60 kg	7 mg		3 mg	10 mg	72 hours

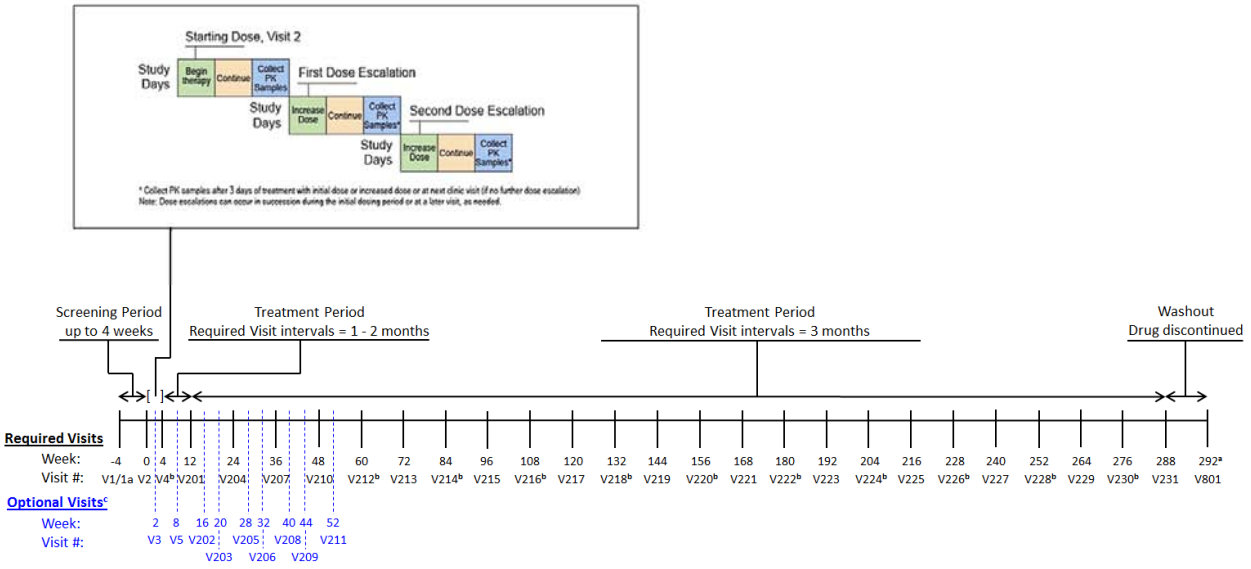
First Dose Escalation

Weight Class[a]	Dose Increase	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Duration[c]
<30 kg	+2 mg	2 mg	2 mg	2 mg	6 mg	72 hours
30 to <40 kg	+2 mg	4 mg	—	4 mg	8 mg	—
40 to <50 kg	+2 mg	5 mg	—	4 mg	9 mg	72 hours
50 to <60 kg	+2 mg	6 mg	—	5 mg	11 mg	72 hours
≥60 kg	+2 mg	7 mg	—	5 mg	12 mg	72 hours

Second Dose Escalation

Weight Class[a]	Evening Dose Increase	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Max/Min Dose (mg/kg)[d]
<30 kg	—	—	—	—	6 mg	0.30/0.2
30 to <40 kg	—	—	—	—	8 mg	0.26/0.2
40 to <50 kg	+1 mg	5 mg	—	5 mg	10 mg	0.25/0.2
50 to <60 kg	+1 mg	6 mg	—	6 mg	12 mg	0.24/0.2
≥60 kg	+2 mg	7 mg	—	7 mg	14 mg	0.23/NA





[a] V801 should occur approximately 28 days after the last dose of investigational product.

[b] These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally.

[c] Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained locally.

Patient Diary and Diary Score

The diary is to be completed daily throughout the study. The diary score is calculated after approximately 7 to 10 days of therapy at a stable dose to assess disease activity and inform the need for an additional dose increase (up to the maximum allowed dose as detailed in Table JAGA.7.1 ~~and Table JAGA.14.2~~) or initiation of steroid weaning as described (if the patient is receiving steroids).

Patients whose average diary scores decrease after receiving the maximum allowable dose level of baricitinib (as defined in Table JAGA.7.1 ~~and Table JAGA.14.2~~), but do not meet the threshold for steroid weaning (for patients receiving steroids at baseline), or an adequate response (do not reach an average daily CANDLE diary score <0.5 or a JDM or SAVI diary score <1.0), may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment. This will not be considered to be a protocol violation.

Section 8. Study Population

Given the severity of these diseases and the absence of other therapeutic options, any patient that does not meet inclusion, exclusion, and/or enrollment criteria may still be considered for enrollment upon consultation with the Sponsor and assessment of the benefits and risks.

Section 8.1.2. Patients with CANDLE-Related Conditions

46) Have organ specific inflammation involving at least one of the following: vasculopathy (such as hypertension, vascular calcifications such as basal ganglia calcifications, or livedo reticularis), metabolic changes (such as lipodystrophy, dyslipidemia, insulin resistance, or intra-abdominal fat deposition), interstitial lung disease, myositis, arthralgia or arthritis, and/or panniculitis.

47) Have high IP-10/CXCL10 levels and/or ~~interferon~~IFN response signature in peripheral blood mononuclear cells being one of the most dysregulated blood signatures.

Section 8.2. Exclusion Criteria

13) Have had symptomatic herpes zoster ~~or herpes simplex~~ infection within 12 weeks prior to entry or during the screening period

14) Have a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster, central nervous system ~~[CNS]~~ involvement, postherpetic neuralgia)

15) Have evidence of active infection, at the time of entry or during the screening period, that in the opinion of the investigator, would pose an unacceptable risk for participating in the study

25) Have a history of chronic alcohol abuse or intravenous ~~(IV)~~ drug abuse within the 2 years prior to entry

8.3.1. Inclusion Criteria

45) For JDM patients, have severe disease as assessed by core set measures (Attachment 7). Severe disease will be assessed as follows: baseline manual muscle testing (~~MMT;~~ within the previous month), with a score no greater than 125 of a possible 150 in conjunction with 2 of the following abnormal core set measures:

- Childhood Health Assessment Questionnaire ~~(CHAQ)~~ or Health Assessment Questionnaire ~~(HAQ)~~ disability index of ≥0.25
- Global extramuscular disease activity score with a minimum value of 1.0 cm on a 10-cm VAS scale (this measure is the physician's composite evaluation and is based on assessments of activity scores on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac scales of the Myositis Disease Activity Assessment Tool ~~(MDAAT)~~ (Attachment 10)

Section 8.3.2. Exclusion from Study Enrollment

31) Have any of the following specific abnormalities on screening laboratory tests:

- AST or ALT >2 × ULN unless the hepatitis is confirmed as resulting from the autoinflammatory condition. If autoinflammatory-associated hepatitis is present, AST or ALT cannot exceed 4 ×ULN. If inflammatory myositis is present or suspected, obtain total and direct bilirubin, aldolase, and gamma-glutamyl transferase ~~(GGT)~~ if not yet done. Elevation in AST and/or ALT is acceptable if ~~GGT~~gamma-glutamyl transferase and total and direct bilirubin are less than 1.5 × ULN and an expert independent of the principal investigator (preferably a hepatologist or gastroenterologist) documents that the elevation is secondary to myositis. Even if inflammatory myositis is considered present, AST or ALT cannot exceed 5 × ULN.

Note: A patient with CANDLE, CANDLE-related condition, or SAVI may be enrolled with ~~a lower hemoglobin level (<10 g/dL), a lower WBC count (<2500 cells/µL), a lower ANC (<1200 cells/µL), or a lower platelet count (<100,000/µL)~~any of the above specific abnormalities on screening laboratory tests if these laboratory abnormalities are considered a feature of the disease. An expert independent of the principal investigator (preferably a hematologist) must evaluate the patient and, in conjunction with the principal investigator, document that the laboratory abnormality is a feature of the underlying CANDLE, CANDLE-related condition, or SAVI condition; the investigator must also consult with the Sponsor before the patient can be enrolled.

32) Have screening thyroid-stimulating hormone ~~(TSH)~~ and/or thyroxine ~~(T4)~~ values outside of the laboratory's reference range and are assessed to be clinically significant. If results are available from testing within 1 month, then the patient will not have to be retested. Patients who are receiving ~~T4~~thyroxine as replacement therapy may participate in the study provided stable therapy has been administered for ≥3 months and ~~TSH~~thyroid-stimulating hormone is within the laboratory's reference range.

35) Have a positive test for hepatitis B defined as (1) positive for hepatitis B surface antigen ~~[HBsAg],~~ or (2) positive for anti-hepatitis B core antibody ~~[HBcAb],~~ but negative for hepatitis B surface antibody ~~[HBsAb]).~~) unless the anti-hepatitis B core antibody is thought to be a false positive result. In the latter case, confirmation of the presence of hepatitis B virus (HBV) by DNA testing is required. An HBV DNA indeterminate result is considered HBV infection.

If results are available from testing within the previous 3 months, then the patient will not have to be retested:

- If any of the hepatitis B tests have an indeterminate result, confirmatory testing will be performed by an alternate method.

36) Have hepatitis C virus (~~HCV) (~~positive for anti-hepatitis C antibody with confirmed presence of ~~HCV~~hepatitis C virus); have evidence of ~~human immunodeficiency virus (~~HIV~~)~~ infection and/or positive HIV antibodies. If results are available from testing within the previous 3 months, then the patient will not have to be retested.

Patients who are entered, but do not meet enrollment criteria, should be discontinued from the study. These patients can be re-entered into the trial (that is, be reconsented) if the investigator believes that the patient might meet enrollment criteria at a future date~~. The investigator should wait approximately 1 month before re-entering a patient into the trial~~, taking into consideration the volume of blood required for rescreening.

Section 8.5.2. Interruption of Investigational Product

~~In the case of abnormal laboratory findings,~~ As listed in Table JAGA.8.1 ~~provides specific guidance for temporarily interrupting treatment, for when treatment may be restarted, and if additional investigations are required.~~, certain situations necessitate a discussion with the Sponsor 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 JAGA.8.1 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.

Table JAGA.8.1.

Hold investigational product if the following laboratory test results occur, unless continuation of investigational product is approved by the Sponsor with documentation:	**If investigational product was stopped, it may be restarted after discussion with the Sponsor or when:**	**Additional instructions:**
WBC count <2000 cells/µL[a]	WBC count ≥2000 cells/µL	None
ANC <1000 cells/µL[a]	ANC >2000 cells/µL (Patients with baseline ANC counts between 1000 and 2000 cells/µL may restart investigational product when values return to baseline.)	None
Lymphocyte count <500 cells/µL[a]	Lymphocyte count ≥500 cells/µL	None
Platelet count <75,000/µL[a]	Platelet count >100,000/µL	None
eGFR <40 mL/min/1.73 m^2 (from serum creatinine)[b]	eGFR ≥40 mL/min/1.73 m^2	None
ALT or AST >5x ULN or ALT or AST >3x ULN and total bilirubin >2x ULN	ALT and AST return to <2x ULN, and investigational product is not considered to be the cause of enzyme elevation.	See Recommended Hepatic Evaluation Guidance Document (Attachment 4).
Hemoglobin <8 g/dL[a]	Hemoglobin ≥8 g/dL	None
HBV DNA ≥29 IU/mL[c]	At the discretion of the investigator after consultation with sponsor.	None
Malignancy	At the discretion of the investigator after consultation with sponsor.	None
Pregnancy	At the discretion of the investigator after consultation with sponsor.	None

[c] If a HBV DNA result of 'target detected' 29 IU/mL or greater, then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study drug 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.

Section 8.5.2.1. Discontinuation from Investigational Product

~~If any of the criteria listed in Section 8.5.2 recur after investigational product is restarted, the patient should be permanently discontinued from investigational product.~~

~~In addition, patients will be permanently discontinued from investigational product if they experience any of the criteria listed in Table JAGA.14.4.~~

Table JAGA.14.4. Criteria for Permanently Discontinuing Investigational Product

Permanently Stop Investigational Product If:	Additional Instructions:
ALT or AST >8 x ULN	See Recommended Hepatic Evaluation Guidance Document (Attachment 4).
ALT or AST >5 x ULN persisting for more than 2 weeks after temporary interruption of investigational product	See Recommended Hepatic Evaluation Guidance Document (Attachment 4).
ALT or AST >3 x ULN and total bilirubin level >2x ULN	See Recommended Hepatic Evaluation Guidance Document (Attachment 4).
ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	See Recommended Hepatic Evaluation Guidance Document (Attachment 4).
WBC count <1000 cells/μL[a]	None
ANC <500 cells/μL[a]	None
Lymphocyte count <200 cells/μL[a]	None
Hemoglobin <6.5 g/dL[a]	None
Symptomatic herpes zoster or herpes simplex	Appropriate treatment should be initiated and patient followed for at least 30 days and/or until infection has resolved.
Patient becomes pregnant	None
Patient develops a malignancy	None
A severe infection occurs that, in the opinion of the investigator, merits the investigational product being discontinued	Appropriate treatment should be initiated and patient followed for at least 30 days and/or until infection has resolved.

[a] Investigational product can be continued if decrease in WBC, ANC, lymphocyte count, platelet count, or hemoglobin is determined to be disease related. An expert independent of the principal investigator (preferably a hematologist) must evaluate the patient and, in conjunction with the principal investigator, determine and document that the laboratory abnormality is related to the underlying disease; the investigator must also consult with the Sponsor to continue the investigational product.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.

Section 9.1. Treatments Administered

All eligible patients will receive treatment with baricitinib as a twice-daily dose, once-daily dose, or multiple divided doses (as described in Section 7.1).

Section 9.2. Materials and Supplies

- Tablets containing 2 mg of baricitinib

Investigational product will be dispensed to the patient at the investigator's study site. As needed, preparation instructions will be provided by the clinical site.

Section 9.4. Rationale for Selection of Doses in the Study

Dose escalation according to Table JAGA.7.1 ~~or Table JAGA.14.2~~ will be performed up to the maximum allowable dose level, as long as there are no safety concerns that would preclude increasing the dose.

The dose escalation parameters specified in Table JAGA.7.1 ~~and Table JAGA.14.2~~ are supported by PK results following baricitinib treatment of the first 2 CANDLE patients (Table JAGA.9.1), as well as results from a Phase 2b study in RA patients.

Improvements in patients with RA, including significant improvement in ~~ACR~~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, improvements in clinical status were only observed upon achieving a stable 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 autoinflammatory syndromes appears to require higher concentrations of DMARDS (~~R~~ Goldbach-Mansky~~, personal communication~~ et al. 2006) for adequate disease management.

Table JAGA.14.5. Preliminary ~~PK~~Pharmacokinetics of Baricitinib in CANDLE 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 or equal to 2 mg (or 0.1 mg/kg) to approach therapeutic levels.

The dose escalation based on the new body weight should be according to ~~Table JAGA.7.1 and Table JAGA.14.2~~Table JAGA.7.1.

Section 9.6. Continued Access to Investigational Product

Patients may receive baricitinib for up to ~~260~~288 weeks under the terms of this study.

Section 9.8. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication ~~CRF~~eCRF.

Section 10.2.1. Adverse Events

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to study procedures are reported to Lilly or designee.

In addition, all AEs occurring after the patient receives the first dose of investigational product must be reported to Lilly or its designee via ~~CRFs (eCRF).~~eCRFs.

Section 10.2.1.1. Serious Adverse Events

~~Serious adverse event~~SAE collection begins after the patient has signed informed consent and has received investigational product.

~~Serious adverse events~~SAEs occurring after a patient has taken the last dose of investigational product will be collected in the pharmacovigilance system and the clinical data-collection database for 28 days after the last dose of investigational product, regardless of the investigator's opinion of causation.

~~Serious adverse events~~SAEs that could be expected in the study population independent of drug exposure will be assessed by the Sponsor in aggregate periodically during the course of the trial are not currently defined.

Section 10.2.1.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the ~~IB~~Investigator's Brochure and that the investigator identifies as related to investigational product or procedure.

Section 10.2.1.2. Adverse Events of Special Interest

Adverse events of special interest ~~(AESIs)~~ include the following:

Patients with these events will be identified using the same criteria presented in Section 8.5.2 for the interruption of investigational product (Table JAGA.8.1) with the exception of anemia, which will be ~~identified using~~defined as a hemoglobin <6.5 g/dL~~the same criteria presented in Section 8.5.2.1 for the discontinuation of investigational product (Table JAGA.8.2)~~, and thrombocytosis, which will be defined as a platelet count >600,000/µL.

Section 10.2.2.1. Electrocardiograms

~~All ECGs collected after screening will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, for immediate patient management.~~

~~Electrocardiograms will also be collected prior to the first dose of a dose escalation, every 3 months while on a stable dose of baricitinib and at the study closeout visit.~~

~~If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG that is printed at the time of evaluation.~~

Section 10.2.2.4. Chest X-Ray and Tuberculosis Testing

In addition, patients will be tested at screening for evidence of active or latent TB indicated by a positive PPD TB skin test response (≥5 mm induration, between approximately 2 and 3 days after test application [visits as indicated on the Study Schedule, Attachment 1], regardless of Bacille Calmette-Guérin ~~[BCG]~~ vaccination history).

Section 10.2.2.5. Liver-Function Monitoring

Liver-function monitoring will occur frequently throughout the study. If elevations in ALT/AST or total bilirubin occur, the patient should be closely observed as described in Table JAGA.8.1 and ~~Table JAGA.14.4 and~~ the Recommended Hepatic Evaluation Guidance Document (Attachment 4).

Section 10.2.2.6. Pulmonary Function Monitoring for SAVI Patients

Monitoring may include vital signs, pulse oximetry, imaging, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide ~~(DLCO).~~.

Section 10.3.2. Samples for Drug Concentration Measurements

Pharmacokinetics

~~CANDLE Patients.~~ ~~Up to 18 venous~~Venous blood samples for the measurement of baricitinib concentrations ~~may~~will be collected from ~~CANDLE~~all patients enrolled in the study.

Table JAGA.10.1 Pharmacokinetic Sampling – ~~CANDLE Patients~~

Sampling at Beginning of Treatment and at Each Dose Increase		
Day 1, Start of therapy or day of dose increase	Baricitinib administered at initial dose or baricitinib dose increased (Table JAGA.7.1)	
Day 2	Continue baricitinib	
Day 3 or next clinic ~~visit~~ visit[1] (if no further dose increase)	Continue baricitinib	Collect 4 PK samples at morning dose: • Pre-morning-dose • 1 hour post-morning-dose • 1.5 hours post-morning-dose • 4 hours post-morning-dose Collect 2 PK samples at evening dose: • Pre-evening-dose • 1.5 hours post-evening-dose

Abbreviations: ~~CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature;~~ PK = pharmacokinetic.

~~**Non-CANDLE Patients.** Up to 16 venous blood samples for the measurement of baricitinib concentrations may be collected from non-CANDLE patients enrolled in the study. Samples will be collected after beginning baricitinib therapy and at each dose increase at the time points shown in Table JAGA.14.6.~~

Table JAGA.14.6. Pharmacokinetic Sampling – Non-CANDLE Patients

Sampling at Beginning of Treatment		
Day 1, Start of therapy	Begin once daily baricitinib dose (Table JAGA.14.2)	
Day 2	Continue baricitinib	
Day 3 or next clinic visit (if no further dose increase)	Continue baricitinib	Collect 4 PK samples: • Pre-morning dose • 1 hour post-morning dose • 1.5 hours post-morning dose • 4 hours post-morning dose
Sampling at Each Dose Increase		
Day 1, Increase dose	Current baricitinib dose combined to a single morning dose, if divided dose administered; add evening dose (Table JAGA.14.2)	
Day 2	Continue baricitinib morning and evening dose	
Day 3 or next clinic visit (if no further dose increase)	Continue baricitinib morning and evening doses	Collect 4 PK samples at morning dose: • Pre-morning dose • 1 hour post-morning dose • 1.5 hours post-morning dose • 4 hours post-morning dose Collect 2 PK samples at evening dose: • Pre-evening dose • 1.5 hours post-evening dose

Abbreviations: CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; PK = pharmacokinetic.

[1] If PK samples cannot be processed within the specified time after collection, the PK samples may be collected on the next business day. For all PK samples, the actual date and exact timing (24-hour clock) of PK sample collection and the date, time, and dosage amount of the last 2 doses prior to the PK sample should be recorded.

Pharmacokinetic PK samples must be collected each time the baricitinib dose is increased. If a patient has an adequate response to treatment at a lower dose than the maximum dose, but becomes unresponsive at a later time, the schedule of dose increases and PK sampling can be resumed. If a patient's daily dose is divided into multiple doses, an additional PK sample may be collected pre-dose for each additional dose. For example, a CANDLE patient receiving twice daily dosing who has their total daily dose divided into 3 doses may have a pre-dose PK sample collected before each of the third dosethree doses.

For all PK samples taken, the actual date and exact timing (24-hour clock) of PK sample collection and the date and time of the last 2 doses prior to the PK sample should be recorded.

Plasma samples will be kept frozen at approximately –20º C to –80º C until the time of the assay. Plasma samples will be assayed for baricitinib concentration using a validated liquid chromatography with tandem mass spectrometry method at a laboratory approved by the Sponsor. ~~Pharmacokinetic~~PK samples may also be assayed for additional exploratory analyses. See also Section 12.2.6.1.

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

Section 10.4. Appropriateness of Measurements

The use of the diary score as a measure of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in autoinflammatory conditions conducted by investigators at the National Institutes of Health ~~(NIH).~~.

Section 11. Data Quality Assurance

- sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the ~~CRFs~~eCRFs, and study procedures.
- review and evaluate ~~CRF~~eCRF data and use standard computer edits to detect errors in data collection

Section 11.1. Data Capture System

~~Case report form (CRF)~~eCRF data will be encoded and stored in a clinical trial database.

Any data for which paper documentation provided by the patient or parent 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 or parent may include, for example, a paper diary to collect patient-reported outcome ~~(PRO)~~ measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Section 12.2.4. Concomitant Therapy

Concomitant therapy will be recorded at each visit and will be classified according to the World Health Organization ~~(WHO)~~ drug dictionary. Concomitant therapy will be reported in patient listings.

Section 12.2.6.1. Pharmacokinetic/Pharmacodynamic Analyses

~~Pharmacokinetic~~PK samples are being taken to ensure drug concentrations do not exceed exposures previously studied in adults following multiple dosing. ~~Formal~~Population PK~~/PD~~ analysis will ~~not~~ be conducted ~~based on the sparse timing of~~to characterize PK ~~sampling from 1 patient, but~~in patients with CANDLE and SAVI. PK/PD analysis or other analysis may also be ~~used to guide dose escalation/adjustment where applicable.~~conducted if deemed appropriate.

Section 13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonization ~~(ICH)~~ guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

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 current ~~IB~~Investigator's Brochure or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae

Section 13.3. Regulatory Considerations

This study will be conducted in accordance with:

(1) 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

(2) the ~~ICH~~International Conference on Harmonization GCP Guideline [E6]

Section 14. References

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Attachment 1. Protocol I4V-MC-JAGA Study Schedule

	Screening		Initial Dosing Period	Treatment							
Visit number	1	1a	2	3	4	5	201	2xx	2xx	Early Termination	Safety Closeout
Weeks from enrollment	−4 to -5		0	2	4	8	12	16 to 52	65 to 260	–	264
Number of days at visit	28 to 2		Variable[p]	1	1	1	1	1	1	1	1
Visit window (days)[n]	–		±2	±2	±2	±2	±2	±2	±5	–	±5
Informed consent	X										
Demographic characteristics	X										
Height	X		X	X	X	X	X	X	X	X	X
Weight	X		X	X	X	X	X	X	X	X	X
Administer tuberculosis test	X[k]										
Read tuberculosis test		X									
Chest x-ray	X[a]										
Electrocardiogram	X						X	X[l]	X	X	X
Review inclusion/exclusion criteria	X										
Medical history	X										
Physical examination	X										
Assessment of JDM core set measures[o]	X										
Vital signs	X		X	X	X	X	X	X	X	X	X
Diary Scores	X		X[b]	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X		X
Preexisting conditions	X										
Adverse events			X	X	X	X	X	X	X	X	X
Investigational drug dose modifications			X[h]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]		

	Screening		Initial Dosing Period	Treatment							
Visit number	1	1a	2	3	4	5	201	2xx[e]	2xx[f]	Early Termination	Safety Closeout
Weeks from enrollment	−4 to −5		0	2	4	8	12	16 to 52	65 to 260	–	264
Number of days at visit	28 to 2		Variable[p]	1	1	1	1	1	1	1	1
Visit window (days)[n]	–		±2	±2	±2	±2	±2	±2	±5	–	±5
Investigational product returned and compliance assessed				X	X	X	X	X	X		
Laboratory											
Hematology	X		X[i]	X	X	X	X	X	X	X	X
Serum chemistry	X		X[i]	X	X	X	X	X	X	X	X
Fasting lipid panel	X					X	X	X	X	X	
Calculated creatinine clearance	X		X[i]	X	X	X	X	X	X	X	X
Urinalysis	X		X[i]	X	X	X	X	X	X	X	X
HbsAg, HbcAb, HbsAb	X[j]										
Hepatitis C antibody	X[j]										
HIV	X[j]										
Thyroid stimulating hormone	X[k]										
Serum pregnancy test[d]	X										
Urine pregnancy test[d]			X	X	X	X	X	X	X	X	X
Serum baricitinib concentration[e]			X	X	X	X	X	X	X		
Pulmonary function tests (SAVI patients only)[q]	X		X	X	X	X	X	X	X	X	

a. If a chest x-ray has not been performed in the 6 months prior to screening visit.

b. Requires at least 2 weeks of diary scores prior to beginning investigational product

e. Baricitinib concentration samples will be collected as described in Section 10.3.2. Samples will be collected after Visit 2 only if patient has a dose escalation (see Table JAGA.7.1 and Table JAGA.14.2).

Footnotes continued on next page.

Footnotes continued from previous page.

d 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 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.

e Visits occur at approximately 4-week intervals during Weeks 16 through 52.

f Visits occur at approximately 13-week intervals during Weeks 65 through 260.

h Each time study dose is adjusted during Visit 2, this CRF will be completed.

i Collect prior to each dose escalation. Investigator will review to ensure dose escalation is appropriate. Collect prior to the last dose given at Visit 2.

j If results are available from testing within the previous 3 months, then the patient will not have to be retested.

k If results are available from testing within 1 month, then the patient will not have to be retested.

l Complete every 3 months.

m See dose escalation schedule (Table JAGA.7.1 and Table JAGA.14.2). Each time study dose is adjusted, this CRF will be completed. Collect samples for chemistry, hematology, and urinalysis 2 weeks after final dose increase. Collect PK samples as described in Section 10.3.2.

n Every effort should be made to schedule patient visits within the allowable visit window; however, if a patient visit is scheduled outside the visit window, it will not be considered a protocol violation.

o Juvenile dermatomyositis patients only.

p Visit 2 encompases the initial dosing period and can vary in time depending on whether the patient progresses through the first and second dose escalation during this period. Four days is the minimum time.

q Pulmonary function tests are required for SAVI patients only. Pulmonary function tests may include vital signs, pulse oximetry, imaging, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide (DLCO). During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased.

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Informed consent		X										
Demographic characteristics		X										
Height		X		X	X	X	X	X	X	X	X	X
Weight		X		X	X	X	X	X	X	X	X	X
Administer tuberculosis test		X[f]										
Read tuberculosis test			X									
Chest x-ray		X[g]										
Electrocardiogram (ECG)		X										
Review inclusion/exclusion criteria		X										
Medical history		X										
Physical examination		X										
Assessment of JDM core measures[h]		X										
Vital signs		X		X	X	X	X	X	X	X	X	X
Diary Scores		X		X[i]	X	X	X	X	X	X	X	X
Concomitant medications		X		X	X	X	X	X	X	X	X	X
Preexisting conditions		X										

Adverse events			X	X	X	X	X	X	X	X	X

(continued)

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4**[q]		**201**	**204, 207, 210**	**212**[q]**, 213, 214**[q]**, 215, 216**[q]**, 217, 218**[q]**, 219, 220**[q]**, 221, 222**[q]**, 223, 224**[q]**, 225, 226**[q]**, 227, 228**[q]**, 229, 230**[q]**, 231**	**ET**[a]	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52**[b]	**60 to 288**[c]	**–**	**292**
Number of days at visit		**28 to 2**		**Variable**[d]	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Investigational drug dose modifications				X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]		
Investigational product returned and compliance assessed					X	X	X	X	X	X		
Laboratory												
Hematology		X		X[l]	X	X	X	X	X	X	X	X
Serum chemistry		X		X[l]	X	X	X	X	X	X	X	X
Fasting lipid panel		X					X	X	X	X	X	
Urinalysis		X		X[l]	X	X	X	X	X	X	X	X
HbsAg, HbcAb, HbsAb		X[m]										
Hepatitis C antibody		X[m]										
HIV		X[m]										
Thyroid stimulating hormone		X[f]										
Serum pregnancy test[n]		X										
Urine pregnancy test[n]				X	X	X	X	X	X	X	X	X

Serum baricitinib concentration[o]			X	X	X	X	X	X	X		
Pulmonary function tests (SAVI patients only)[p]	X		X	X	X	X	X	X	X	X	

Abbreviations and footnotes on next page.

Abbreviations: ET = early termination; JDM = juvenile dermatomyositis; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibiody; HBsAb = hepatitis B surface antibody; HIV = human immunodeficiency virus; SAVI = STING-associated vasculopathy with onset during infancy.

a Early termination visit is required if early termination occurs.
b Visits occur at approximately 4-week intervals during Weeks 16 through 52 (including both required and optional visits)
c Visits occur at approximately 12-week intervals during Weeks 60 through 288.
d Visit 2 encompasses the initial dosing period and can vary in time depending on whether the patient progresses through the first and second dose escalation during this period. Four days is the minimum time.
e Every effort should be made to schedule patient visits within the allowable visit window; however, if a patient visit is scheduled outside the visit window, it will not be considered a protocol violation.
f If results are available from testing within 1 month, then the patient will not have to be retested.
g If a chest x-ray has not been performed in the 6 months prior to screening visit.
h Juvenile dermatomyositis patients only.
i At least 2 weeks of diary scores are required prior to beginning investigational product.
j Each time study dose is adjusted during Visit 2, this eCRF will be completed.
k See dose escalation schedule (**Table JAGA.7.1**). Each time study dose is adjusted, this eCRF will be completed. Collect samples for chemistry, hematology, and urinalysis 2 weeks after final dose increase. Collect PK samples as described in Section **10.3.2**.
l Collect prior to each dose escalation. Investigator will review to ensure dose escalation is appropriate. Collect prior to the last dose given at Visit 2.
m If results are available from testing within the previous 3 months, then the patient will not have to be retested.
n 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 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
o Baricitinib concentration samples will be collected as described in Section **10.3.2**. Samples will be collected after Visit 2 only if patient has a dose escalation (see **Table JAGA.7.1**).
p Pulmonary function tests are required for SAVI patients only. Pulmonary function tests may include vital signs, pulse oximetry, imaging, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide (DLCO). During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased.
q These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2.
r Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained locally.

Attachment 2. Protocol I4V-MC-JAGA Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b,c]	**Serum Chemistry[a,b]**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin[c]
Mean cell volume (MCV)	Direct bilirubin[c]
Mean cell hemoglobin concentration (MCHC)	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT/SGPT)[c]
Reticulocyte	Aspartate aminotransferase (AST/SGOT)[c]
Absolute counts of:	Blood urea nitrogen (BUN)[c]
Neutrophils, segmented	Creatinine[c]
Neutrophils, juvenile (bands)	Calcium
Lymphocytes	Glucose
Monocytes	Albumin
Eosinophils	Total protein
Basophils	Creatine phosphokinase (CPK)
Platelets	Uric acid
Cell Morphology	Gamma glutamyl transferase (GGT)
	Aldolase[d~~i~~]
Lipid[e]	~~Calculated creatinine clearance[e]~~
Total cholesterol (TC)	~~Estimated glomerular filtration rate (eGFR)~~
Low-density lipoprotein (LDL)	
High-density lipoprotein (HDL)	**Other Tests[a]**
Triglycerides	Hepatitis B Surface antigen (HBsAg)[~~f~~g]
	Anti-Hepatitis B Core antibody (HBcAb)[~~f~~g]
Urinalysis[a,b,~~d~~f]	Hepatitis B Surface antibody (HBsAb)[~~f~~g]
Color	Hepatitis B Virus DNA[g]
Specific gravity	~~Hepatitis C antibody[e,]~~
	Human immunodeficiency virus (HIV)[g~~f~~]
pH	Hepatitis C antibody[h~~e~~]
Protein	Thyroid-stimulating hormone (TSH)[g~~f~~]
Glucose	Thyroxine (T4)[g~~f~~]
Ketones	Pregnancy Test[i~~e~~]
Bilirubin	QuantiFERON®-TB Gold[g~~,i~~h]
Urobilinogen	Baricitinib serum concentration
Blood	
Leukocyte esterase	
Nitrite	

Abbreviations: ~~eGFR = estimated glomerular filtration rate;~~ PPD = purified protein derivative; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis; WBC = white blood cells.

Footnotes on next page.

a Assayed by local clinical laboratory.

b Unscheduled blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator.

~~e~~c If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2.

d Perform if inflammatory myositis is present.

e Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to test.

~~d~~f Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.

~~e The calculated creatinine clearance will be determined each time a serum creatinine sample is collected using an age-appropriate equation.~~

~~Footnotes continued on next page.~~

~~Footnotes continued from previous page.~~

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

~~g~~h A positive hepatitis C antibody result will be confirmed with a positive hepatitis C virus result.

i For all women of childbearing potential, a serum pregnancy test will be performed at ~~Visits~~Visit 1 and a urine pregnancy test (local laboratory) will be performed at Visit 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.

~~h~~j The QuantiFERON®-TB Gold 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. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

~~i Perform if inflammatory myositis is present.~~

Attachment 3. Protocol I4V-MC-JAGA Sampling Summary

This table summarizes the maximum number of samples and volumes for all sampling and tests during the entire ~~264~~292-week study period, including the optional visits. The volume of blood drawn is less than the maximum recommended volume in both the National Institutes of Health ~~(NIH)~~ and World Health Organization guidelines (Howie 2011) for pediatric patients. Fewer samples may actually be taken, but this will not require a protocol amendment.

		~~CANDLE Patients~~		~~Non-CANDLE Patients~~	
	~~Maximum Volume per Sample~~	~~Maximum Number of Samples~~	~~Maximum Total Volume~~	~~Maximum Number of Samples~~	~~Maximum Total Volume~~
~~**<20 kg**~~					
~~— Screening laboratory tests~~	~~7 mL~~	~~1~~	~~7 mL~~	~~1~~	~~7 mL~~
~~— Standard laboratory tests~~	~~7 mL~~	~~31~~	~~217 mL~~	~~32~~	~~224 mL~~
~~— Drug concentration~~	~~1.2 mL~~	~~6~~	~~7.2 mL~~	~~10~~	~~12 mL~~
~~**Total volume of blood**~~			~~**231.2 mL**~~		~~**243 mL**~~
~~**20 to <30 kg**~~					
~~— Screening laboratory tests~~	~~7 mL~~	~~1~~	~~7 mL~~	~~1~~	~~7 mL~~
~~— Standard laboratory tests~~	~~7 mL~~	~~32~~	~~224 mL~~	~~33~~	~~231 mL~~
~~— Drug concentration~~	~~1.2 mL~~	~~12~~	~~14.4 mL~~	~~16~~	~~19.2 mL~~
~~**Total volume of blood**~~			~~**245.4 mL**~~		~~**257.2 mL**~~
~~**30 to <40 kg**~~					
~~— Screening laboratory tests~~	~~7 mL~~	~~1~~	~~7 mL~~	~~1~~	~~7 mL~~
~~— Standard laboratory tests~~	~~7 mL~~	~~32~~	~~224 mL~~	~~33~~	~~231 mL~~
~~— Drug concentration~~	~~1.2 mL~~	~~12~~	~~14.4 mL~~	~~16~~	~~19.2 mL~~
~~**Total volume of blood**~~			~~**245.4 mL**~~		~~**257.2 mL**~~
~~**40 to <50 kg**~~					
~~— Screening laboratory tests~~	~~7 mL~~	~~1~~	~~7 mL~~	~~1~~	~~7 mL~~
~~— Standard laboratory tests~~	~~7 mL~~	~~33~~	~~231 mL~~	~~33~~	~~231 mL~~
~~— Drug concentration~~	~~1.2 mL~~	~~18~~	~~21.6 mL~~	~~16~~	~~19.2 mL~~
~~**Total volume of blood**~~			~~**259.6 mL**~~		~~**257.2 mL**~~
~~**50 to <60 kg**~~					
~~— Screening laboratory tests~~	~~7 mL~~	~~1~~	~~7 mL~~	~~1~~	~~7 mL~~
~~— Standard laboratory tests~~	~~7 mL~~	~~33~~	~~231 mL~~	~~33~~	~~231 mL~~
~~— Drug concentration~~	~~1.2 mL~~	~~18~~	~~21.6 mL~~	~~16~~	~~19.2 mL~~
~~**Total volume of blood**~~			~~**259.6 mL**~~		~~**257.2 mL**~~

~~(continued)~~

		~~CANDLE Patients~~		~~Non-CANDLE Patients~~	
	~~Maximum Volume per Sample~~	~~Maximum Number of Samples~~	~~Maximum Total Volume~~	~~Maximum Number of Samples~~	~~Maximum Total Volume~~
~~>60 kg~~					
~~Screening laboratory tests~~	~~7 mL~~	~~1~~	~~7 mL~~	~~1~~	~~7 mL~~
~~Standard laboratory tests~~	~~7 mL~~	~~33~~	~~231 mL~~	~~33~~	~~231 mL~~
~~Drug concentration~~	~~1.2 mL~~	~~18~~	~~21.6 mL~~	~~16~~	~~19.2 mL~~
~~**Total volume of blood**~~			~~**259.6 mL**~~		~~**257.2 mL**~~

	All Patients		
	Maximum Volume per Sample	**Maximum Number of Samples**	**Maximum Total Volume**
<30 kg			
Screening laboratory tests	7 mL	1	7 mL
Standard laboratory tests[a]	7 mL	36	252 mL
Drug concentration[b]	1.2 mL	12	14.4 mL
Total volume of blood			**273.4 mL**
30 to <40 kg			
Screening laboratory tests	7 mL	1	7 mL
Standard laboratory tests[a]	7 mL	36	252 mL
Drug concentration[b]	1.2 mL	12	14.4 mL
Total volume of blood			**273.4 mL**
40 to <50 kg			
Screening laboratory tests	7 mL	1	7 mL
Standard laboratory tests[a]	7 mL	37	259 mL
Drug concentration[b]	1.2 mL	18	21.6 mL
Total volume of blood			**287.6 mL**
50 to <60 kg			
Screening laboratory tests	7 mL	1	7 mL
Standard laboratory tests[a]	7 mL	37	259 mL
Drug concentration[b]	1.2 mL	18	21.6 mL
Total volume of blood			**287.6 mL**

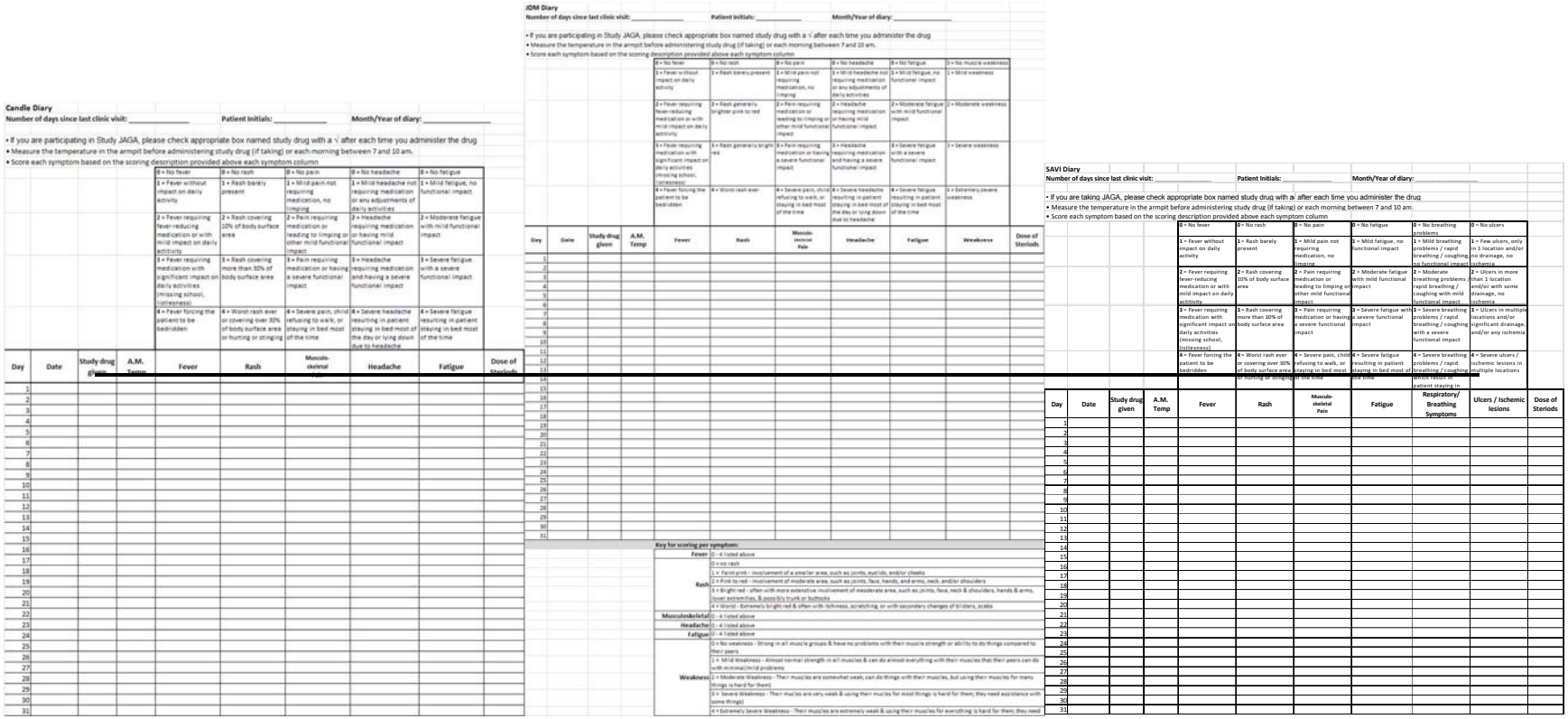
>60 kg			
Screening laboratory tests	7 mL	1	7 mL
Standard laboratory tests[a]	7 mL	37	259 mL
Drug concentration[b]	1.2 mL	18	21.6 mL
Total volume of blood			**287.6 mL**

~~Abbreviations: CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature.~~
~~Note:~~ [a] Standard laboratory tests include chemistry, hematology, and lipid panels.
[b] The protocol allows for additional dose escalations with sponsor consultation and approval. These potential additional dose escalations would require additional drug concentration samples not reflected here.

Attachment 4. Protocol I4V-MC-JAGA Recommended Hepatic Evaluation Guidance Document

Investigators are encouraged to use clinical judgment and may consult with the Lilly ~~CRP~~clinical research physician for further clarification as necessary.

Attachment 5. Protocol I4V-MC-JAGA Patient Diaries



Candle Diary

Number of days since last clinic visit: _____ Patient Initials: _____ Month/Year of diary: _____

- If you are participating in Study JAGA, please check appropriate box named study drug with a √ after each time you administer the drug
- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

	0 = No fever	0 = No rash	0 = No pain	0 = No headache	0 = No fatigue
	1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild headache not requiring medication or any adjustments of daily activities	1 = Mild fatigue, no functional impact
	2 = Fever requiring fever-reducing medication or with mild impact on daily activity	2 = Rash covering 10% of body surface area	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Headache requiring medication or having mild functional impact	2 = Moderate fatigue with mild functional impact
	3 = Fever requiring medication with significant impact on daily activities (missing school, listlessness)	3 = Rash covering more than 30% of body surface area	3 = Pain requiring medication or having a severe functional impact	3 = Headache requiring medication and having a severe functional impact	3 = Severe fatigue with a severe functional impact
	4 = Fever forcing the patient to be bedridden	4 = Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	4 = Severe fatigue resulting in patient staying in bed most of the time

Day	Date	Study drug given	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Dose of Steriods
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
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25									
26									
27									
28									
29									
30									
31									

JDM Diary

Number of days since last clinic visit: _____ Patient Initials: _____ Month/Year of diary: _____

- If you are participating in Study JAGA, please check appropriate box named study drug with a √ after each time you administer the drug
- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

	0 = No fever	0 = No rash	0 = No pain	0 = No headache	0 = No fatigue	0 = No muscle weakness
	1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild headache not requiring medication or any adjustments of daily activities	1 = Mild fatigue, no functional impact	1 = Mild weakness
	2 = Fever requiring fever-reducing medication or with mild impact on daily activity	2 = Rash generally brighter pink to red	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Headache requiring medication or having mild functional impact	2 = Moderate fatigue with mild functional impact	2 = Moderate weakness
	3 = Fever requiring medication with significant impact on daily activities (missing school, listlessness)	3 = Rash generally bright red	3 = Pain requiring medication or having a severe functional impact	3 = Headache requiring medication and having a severe functional impact	3 = Severe fatigue with a severe functional impact	3 = Severe weakness
	4 = Fever forcing the patient to be bedridden	4 = Worst rash ever	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	4 = Severe fatigue resulting in patient staying in bed most of the time	4 = Extremely severe weakness

Day	Date	Study drug given	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Fatigue	Dose of Steriods
1								
2								
3								
4								
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29								
30								
31								

Key for scoring per symptom:

Fever	0 - 4 listed above
Rash	0 = no rash 1 = Faint pink - involvement of a smaller area, such as joints, eyelids, and/or cheeks 2 = Pink to red - involvement of moderate area, such as joints, face, hands, and arms, neck, and/or shoulders 3 = Bright red - often with more extensive involvement of mesoderate area, such as joints, face, neck & shoulders, hands & arms, lower extremities, & possibly trunk or buttocks 4 = Worst - Extremely bright red & often with itchiness, scratching, or with secondary changes of blisters, scabs
Musculoskeletal	0 - 4 listed above
Headache	0 - 4 listed above
Fatigue	0 - 4 listed above
Weakness	0 = No weakness - Strong in all muscle groups & have no problems with their muscle strength or ability to do things compared to their peers 1 = Mild Weakness - Almost normal strength in all muscles & can do almost everything with their muscles that their peers can do with minimal/mild problems 2 = Moderate Weakness - Their muscles are somewhat weak, can do things with their muscles, but using their muscles for many things is hard for them) 3 = Severe Weakness - Their muscles are very weak & using their muscles for most things is hard for them, they need assistance with some things) 4 = Extremely Severe Weakness - Their muscles are extremely weak & using their muscles for everything is hard for them, they need

SAVI Diary

Number of days since last clinic visit: _____ Patient Initials: _____ Month/Year of diary: _____

- If you are taking JAGA, please check appropriate box named study drug with a √ after each time you administer the drug
- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

	0 = No fever	0 = No rash	0 = No pain	0 = No fatigue	0 = No breathing problems	0 = No ulcers
	1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild fatigue, no functional impact	1 = Mild breathing problems / rapid breathing / coughing, no functional impact	1 = Few ulcers, only in 1 location and/or no drainage, no ischemia
	2 = Fever requiring fever-reducing medication or with mild impact on daily activity	2 = Rash covering 10% of body surface area	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Moderate fatigue with mild functional impact	2 = Moderate breathing problems / rapid breathing / coughing with mild functional impact	2 = Ulcers in more than 1 location and/or with some drainage, no ischemia
	3 = Fever requiring medication with significant impact on daily activities (missing school, listlessness)	3 = Rash covering more than 30% of body surface area	3 = Pain requiring medication or having a severe functional impact	3 = Severe fatigue with a severe functional impact	3 = Severe breathing problems / rapid breathing / coughing with a severe functional impact	3 = Ulcers in multiple locations and/or significant drainage, and/or any ischemia
	4 = Fever forcing the patient to be bedridden	4 = Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe fatigue resulting in patient staying in bed most of the time	4 = Severe breathing problems / rapid breathing / coughing, unable to speak / talk or patient staying in	4 = Severe ulcers / ischemic lesions in multiple locations

Day	Date	Study drug given	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Fatigue	Respiratory/ Breathing Symptoms	Ulcers / Ischemic lesions	Dose of Steriods
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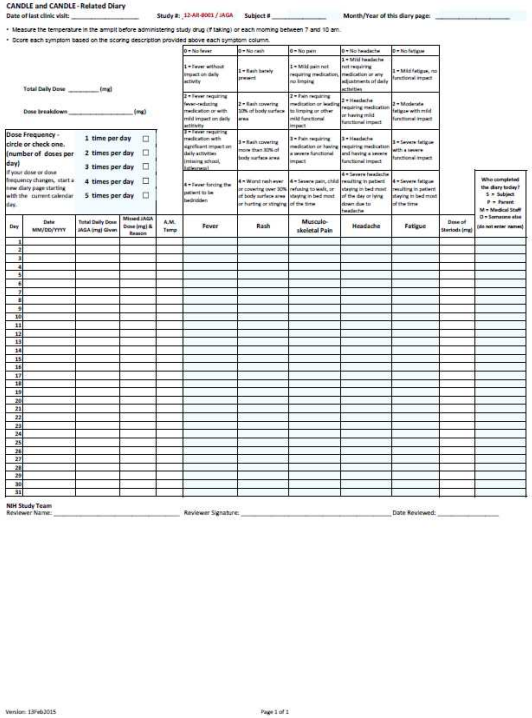

CANDLE and CANDLE -Related Diary

Date of last clinic visit: _____ Study #: 12-AR-8001 / JAGA Subject # _____ Month/Year of this diary page: _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column.

Total Daily Dose _____ (mg)

Dose breakdown _____ (mg)

	0 = No fever	0 = No rash	0 = No pain	0 = No headache	0 = No fatigue
	1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild headache not requiring medication or any adjustments of daily activities	1 = Mild Fatigue, no functional impact
	2 = Fever requiring fever-reducing medication or with mild impact on daily activity	2 = Rash covering 10% of body surface area	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Headache requiring medication or having mild functional impact	2 = Moderate fatigue with mild functional impact
	3 = Fever requiring medication with significant impact on daily activities (missing school, takeaway)	3 = Rash covering more than 30% of body surface area	3 = Pain requiring medication or having a severe functional impact	3 = Headache requiring medication and having a severe functional impact	3 = Severe fatigue with a severe functional impact
	4 = Fever forcing the patient to be bedridden	4 = Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	4 = Severe fatigue resulting in patient staying in bed most of the time

Dose Frequency - circle or check one. (number of doses per day)
If your dose or dose frequency changes, start a new diary page starting with the current calendar day.
1 time per day ☐
2 times per day ☐
3 times per day ☐
4 times per day ☐
5 times per day ☐

Who completed the diary today? S = Subject P = Parent M = Medical Staff O = Someone else (do not enter names)

Day	Date MM/DD/YYYY	Total Daily Dose JAGA (mg) Given	Missed JAGA Dose (mg) & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Dose of Steriods (mg)	Who completed the diary today? S = Subject P = Parent M = Medical Staff O = Someone else (do not enter names)
1											
2											
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31											

NIH Study Team
Reviewer Name: _____ Reviewer Signature: _____ Date Reviewed: _____

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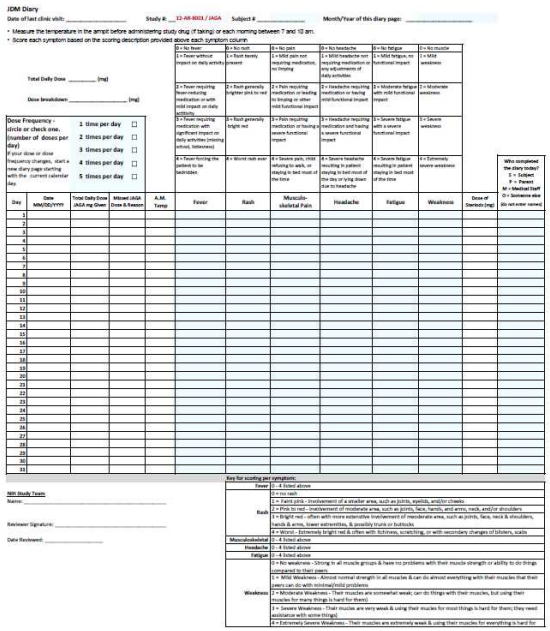

JDM Diary

Date of last clinic visit: _____ Study #: _____12-AR-8001 / JAGA Subject # _____ Month/Year of this diary page: _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column.

Total Daily Dose _____ (mg)

Dose breakdown _____ (mg)

	0 = No fever	0 = No rash	0 = No pain	0 = No headache	0 = No fatigue	0 = No muscle
	1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild headache not requiring medication or any adjustments of daily activities	1 = Mild fatigue, no functional impact	1 = Mild weakness
	2 = Fever requiring fever-reducing medication or with mild impact on daily activity	2 = Rash generally brighter pink to red	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Headache requiring medication or having mild functional impact	2 = Moderate fatigue with mild functional impact	2 = Moderate weakness
	3 = Fever requiring medication with significant impact on daily activities (missing school, takeaway)	3 = Rash generally bright red	3 = Pain requiring medication or having a severe functional impact	3 = Headache requiring medication and having a severe functional impact	3 = Severe fatigue with a severe functional impact	3 = Severe weakness
	4 = Fever forcing the patient to be bedridden	4 = Worst rash ever	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	4 = Severe fatigue resulting in patient staying in bed most of the time	4 = Extremely severe weakness

Dose Frequency - circle or check one. (number of doses per day)
If your dose or dose frequency changes, start a new diary page starting with the current calendar day.
1 time per day ☐
2 times per day ☐
3 times per day ☐
4 times per day ☐
5 times per day ☐

Who completed the diary today? S = Subject P = Parent M = Medical Staff O = Someone else (do not enter names)

Day	Date MM/DD/YYYY	Total Daily Dose JAGA mg Given	Missed JAGA Dose & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Weakness	Dose of Steriods (mg)	Who completed the diary today? S = Subject P = Parent M = Medical Staff O = Someone else (do not enter names)
1												
2												
3												
4												
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9												
10												
11												
12												
13												
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27												
28												
29												
30												
31												

Key for scoring per symptom:

Fever	0 – 4 listed above
Rash	0 = no rash 1 = Faint pink – involvement of a smaller area, such as joints, eyelids, and/or cheeks 2 = Pink to red – involvement of moderate area, such as joints, face, hands, and arms, neck, and/or shoulders 3 = Bright red – often with more extensive involvement of moderate area, such as joints, face, neck & shoulders, hands & arms, lower extremities, & possibly trunk or buttocks 4 = Worst – Extremely bright red & often with itchiness, scratching, or with secondary changes of blisters, scabs
Musculoskeletal	0 – 4 listed above
Headache	0 – 4 listed above
Fatigue	0 – 4 listed above
Weakness	0 = No weakness – Strong in all muscle groups & have no problems with their muscle strength or ability to do things compared to their peers. 1 = Mild Weakness – Almost normal strength in all muscles & can do almost everything with their muscles that their peers can do with minimal/mild problems 2 = Moderate Weakness – Their muscles are somewhat weak; can do things with their muscles, but using their muscles for many things is hard for them) 3 = Severe Weakness – Their muscles are very weak & using their muscles for most things is hard for them; they need assistance with some things) 4 = Extremely Severe Weakness – Their muscles are extremely weak & using their muscles for everything is hard for

NIH Study Team
Name: _____
Reviewer Signature: _____
Date Reviewed: _____

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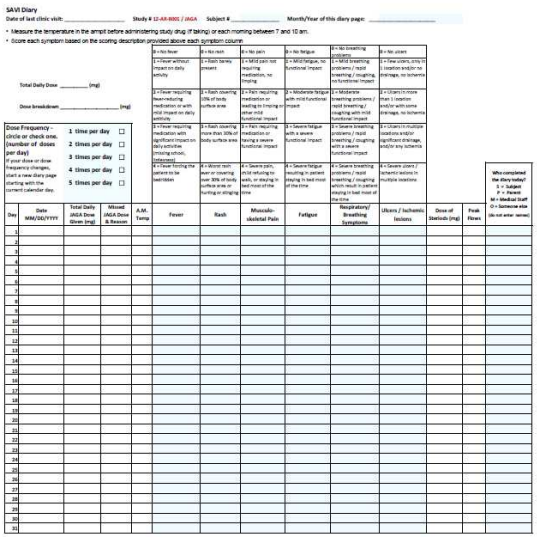

SAVI Diary

Date of last clinic visit: _____ Study # 12-AR-8001 / JAGA Subject # _____ Month/Year of this diary page: _____

- Measure the temperature in the armpit before administering study drug, if taking, or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

Total Daily Dose _____ (mg)

Dose breakdown _____ (mg)

	0 = No fever	0 = No rash	0 = No pain	0 = No fatigue	0 = No breathing problems	0 = No ulcers
	1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild fatigue, no functional impact	1 = Mild breathing problems / rapid breathing / coughing, no functional impact	1 = Few ulcers, only in 1 location and/or no mild rage, no ischemia
	2 = Fever requiring fever-reducing medication or with mild impact on daily activity	2 = Rash covering 10% of body surface area	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Moderate fatigue with mild functional impact	2 = Moderate breathing problems / rapid breathing / coughing with mild functional impact	2 = Ulcers in more than 1 location and/or with some mild rage, no ischemia
	3 = Fever requiring medication with significant impact on daily activities (missing school, takeaway)	3 = Rash covering more than 30% of body surface area	3 = Pain requiring medication or having a severe functional impact	3 = Severe fatigue with a severe functional impact	3 = Severe breathing problems / rapid breathing / coughing with a severe functional impact	2 = Ulcers in multiple locations and/or significant mild rage, and/or any ischemia
	4 = Fever forcing the patient to be bedridden	4 = Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe fatigue resulting in patient staying in bed most of the time	4 = Severe breathing problems / rapid breathing / coughing which result in patient staying in bed most of the time	4 = Severe ulcers / ischemic lesions in multiple locations

Dose Frequency - circle or check one. (number of doses per day)
If your dose or dose frequency changes, start a new diary page starting with the current calendar day.
1 time per day ☐
2 times per day ☐
3 times per day ☐
4 times per day ☐
5 times per day ☐

Who completed the diary today? S = Subject P = Parent M = Medical Staff O = Someone else (do not enter names)

Day	Date MM/DD/YYYY	Total Daily JAGA Dose Given (mg)	Missed JAGA Dose & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Fatigue	Respiratory/ Breathing Symptoms	Ulcers / Ischemic lesions	Dose of Steriods (mg)	Peak Flows	Who completed the diary today? S = Subject P = Parent M = Medical Staff O = Someone else (do not enter names)
1													
2													
3													
4													
5													
6													
7													
8													
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NIH Study Team
Name: _____ Reviewer Signature: _____ Date Reviewed: _____

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Attachment 7. Protocol I4V-MC-JAGA Juvenile Dermatomyositis Core Set Measures

Core Set Measures

Extramuscular Disease	A validated approach that is comprehensive and assesses cutaneous, gastrointestinal, articular, cardiac, and pulmonary activity. Myositis Disease Activity Assessment Tool ~~(MDAAT)~~ has been validated.

Manual Muscle Testing – 8 Designated Muscles

Abbreviations: MMT = Manual Muscle Test – 8 designated muscles.

Leo Document ID = a85f37c7-3226-4de6-8229-8f0984102476

Approver: PPD
Approval Date & Time: 20-Feb-2015 17:10:10 GMT
Signature meaning: Approved

1. Protocol Addendum I4V-MC-JAGA (3.1) Compassionate Use Treatment Protocol I4V-MC-JAGA(r): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Baricitinib (LY3009104)

This addendum is to be performed in addition to all procedures required by protocol I4V-MC-JAGA(r) or any subsequent amendments to that protocol.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Addendum (3) Electronically Signed and Approved by Lilly on 22-Oct-2015.
Revised Protocol Addendum (3.1) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 09-Sep-2016 GMT

2. Table of Contents

Protocol Addendum I4V-MC-JAGA (3.1) Compassionate Use Treatment Protocol I4V-MC-JAGA(r): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Section **Page**

List of Attachments

Attachment **Page**

3. Rationale for Addendum

This addendum applies to sites enrolling patients with Aicardi-Goutières Syndrome (AGS). AGS is a monogenic disorder resulting from loss of function 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). Given that AGS is an interferon-mediated disease, patients with AGS are expected to benefit from JAK1 and JAK2 inhibition and, thus, it may be beneficial to treat them with baricitinib. The purpose of this addendum is to add specific entry and patient assessment criteria for patients with AGS to the existing Protocol I4V-MC-JAGA(r). The addendum is being revised in order to allow for an additional safety procedure (fundoscopy) to be completed as part of the physical examination if, in the opinion of the investigator, it is needed to monitor safety in specific AGS patients.

4. Protocol Additions

The following sections of Protocol I4V-MC-JAGA(r) have been modified in this addendum to allow patients with AGS to be eligible for enrollment at specific sites.

2. Synopsis

Number of Planned Patients/Subjects: Entered: up to 60 Enrolled: up to 60 Completed: up to 60
Objectives: The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, juvenile dermatomyositis (JDM), SAVI, or AGS results in a reduction in the patient's mean daily diary scores as follows: • CANDLE diary: reduction in mean daily score to <0.5 • SAVI diary: reduction in mean daily score to <1.0, exclusive of respiratory/breathing symptom, and a <1.0 increase from baseline in the respiratory/breathing symptom • JDM diary: decrease in mean diary score by 1 point in at least 3 categories • AGS diary: reduction in mean daily score to <0.5.
Diagnosis and Main Criteria for Inclusion and Exclusions: Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder for which there is reason to believe that JAK 1/2 inhibition will be beneficial. One such autoinflammatory disorder is chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. CANDLE syndrome 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). Other patients eligible to be enrolled into this study include those diagnosed with conditions related to CANDLE syndrome involving immune dysregulation: stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), an autoinflammatory syndrome with interferon (IFN) pathway dysregulation, juvenile dermatomyositis (JDM), and Aicardi-Goutières syndrome (AGS).

5. Introduction

The purpose of this open-label, compassionate use, treatment protocol is to provide baricitinib to patients with CANDLE*, CANDLE-related conditions, SAVI,* severe juvenile dermatomyositis (JDM), and Aicardi-Goutières syndrome (AGS) who are not responsive to biologic therapies and who require treatment with high doses of steroids to control systemic signs and symptoms of their condition (or, in the opinion of the investigator, have failed an adequate course of steroids) and are eligible for treatment under this protocol. Baricitinib is an orally administered inhibitor of Janus kinases 1 and 2 (JAK1 and JAK2).

Autoinflammatory Diseases

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

- **Aicardi-Goutières Syndrome (AGS).** 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 (for example, glaucoma, cardiomyopathy, neuropathy, endocrinological problems) in many patients. All available literature sources suggest that the prevalence of AGS is well below 5 in 10,000 persons.

Most 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 in any of the genes encoding the DNA exonuclease TREX1 (TREX1), the three non-allelic components of the RNase H2 endonuclease complex (RNASEH2A, RNASEH2B, and RNASEH2C), the deoxynucleoside triphosphate triphosphohydrolase SAMHD1 (SAMHD1), the double-stranded RNA editing enzyme ADAR (ADAR), and the double-stranded RNA cytosolic sensor IFIH1/MDA5 (IFIH1).

The proteins defective in AGS are all associated with nucleic acid metabolism/sensing. It is hypothesized that six of these proteins are involved in limiting the accumulation (TREX1, the three RNase H2 complex components, SAMHD1), or the nature (ADAR), of intracellular nucleic acid species, a failure of which process 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 interferon-stimulatory nucleic acids, and offers an elegant mechanistic explanation for the phenotypic overlap of AGS with congenital infection and systemic lupus erythematosus (SLE). 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 interferon alpha-mediated immune response and, sometimes, the production of antibodies against self-nucleic acids.

AGS is associated with increased levels of interferon alpha in the cerebrospinal fluid (CSF) and serum. However, interferon alpha levels, and white cell counts, in the CSF 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 CSF sampling, very few serial data are available (that is, systematic interferon alpha activity profiling beyond infancy has not been undertaken).

Indeed, data acquired more recently on more than 200 AGS patients using qPCR analysis of interferon stimulated genes (ISGs) indicates the presence of a so-called "interferon signature" at any age in almost 100% of patients with mutations in TREX1, RNASEH2A, RNASEH2C, SAMHD1, ADAR, and IFIH1. Around 30% of patients with RNASEH2B mutations demonstrated no such upregulation—but as ISG sampling in these studies was usually performed many years after initial diagnosis, it remains possible that all patients exhibit a positive interferon 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 life-long in most patients.

Although some children are affected by the time of birth (that is, the disease has an in utero onset), most experience the onset of disease at some point post-natally, 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, for example, 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 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 here, 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 interferons can have a neurotoxic effect at the cellular level in the absence of obvious neuroimaging changes. Most recently, IFIH1 gain of function 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.

Summary

Patients with CANDLE, CANDLE-related conditions, SAVI, severe JDM, and AGS who are not responsive to at least 1 biologic therapy (except as noted in the inclusion/exclusion criteria), and who require treatment with oral corticosteroids (≥0.15 mg/kg/day of prednisone or its equivalent) to control systemic signs and symptoms of their syndrome (or, in the opinion of the investigator, have failed an adequate course of steroids, except as noted in the inclusion/exclusion criteria), will be candidates for baricitinib treatment. 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 CANDLE, CANDLE-related conditions, SAVI, severe JDM, and AGS for whom biologics have proven to be

ineffective and/or there are no other treatments, thereby offering these patients an alternative compassionate use therapeutic option.

6. Objectives

6.1. Primary Objective

The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, JDM, or AGS results in reduction in the patient's mean daily diary scores as follows:

- CANDLE diary: reduction in mean daily score to <0.5
- SAVI diary: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and respiratory/breathing symptoms score a <1.0 increase from baseline
- JDM diary: reduction in mean score by 1 point in at least 3 categories.
- AGS diary: reduction in mean daily score to <0.5.

7. Investigational Plan

7.1. Summary of Study Design

Continuing Treatment: After the patient has received baricitinib at the target dose level for approximately 14 days, the patient will have an evaluation performed, which will include an assessment of the patient's clinical condition, AEs, and blood tests for safety per the Study Schedule. Safety laboratory assessments will be performed and reviewed by the investigator along with a copy of the patient's diary. AEs and concomitant medications will be assessed over the phone or in person by the study team. Once the patient has reached a stable dose of baricitinib, the same total dose may be administered as equal or unequal divided doses (administered up to 4 doses in a day [24 hours]). If more than 4 doses are needed in 1 day (24 hours), then consultation and agreement with the Sponsor will be required.

1. If the patient is responding adequately to treatment (average diary score <0.5 or <1.0 [CANDLE/AGS or SAVI/JDM diary, respectively]), the patient will continue receiving baricitinib therapy with follow-up appointments according to the Study Schedule. Steroid weaning may begin for patients who are receiving steroids. If the patient is responding to treatment, but has not met the threshold to begin steroid weaning and is experiencing clinically significant adverse effects from steroids, steroid weaning may begin when, in the opinion of the investigator, an adequate response has been achieved.
5. If a patient reaches the maximum allowable dose (or had a dose modification as described in item 3 above [see Protocol I4V-MC-JAGA(r)]) and his or her average diary score has decreased, but has not met the threshold for adequate response/steroid weaning (does not reach an average diary score of <0.5 or <1.0 [CANDLE/AGS or SAVI/JDM diary,

respectively]), the patient may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment.

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 (that is, CANDLE, JDM, SAVI, or AGS). The assessments included in the patient diaries are shown in Attachment 1. Each patient (or caregiver) will complete the diary at approximately the same time every day during the screening period and during the duration of the study. Ideally, the same person will complete the diary each day. During clinic visits, it is preferable that the patient or caregiver complete the patient diary rather than site staff. As this protocol will include patients with a spectrum of clinical symptoms, the investigator will determine which features listed in the diary are present and representative of the disease activity for the individual patient. Only these identified features will be used to determine average diary scores as a treatment outcome for the patient.

For patients with CANDLE, SAVI, or JDM, the patient or caregiver will be instructed to rate each symptom (fever, rash, musculoskeletal pain, and fatigue [all diaries], headache [CANDLE and JDM diaries], weakness [JDM 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]). 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. 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.

The diary is to be completed daily throughout the study. The diary score is calculated after approximately 7 to 10 days of therapy at a stable dose to assess disease activity and inform the need for an additional dose increase (up to the maximum allowed dose as detailed in the clinical protocol I4V-MC-JAGA(r)) or initiation of steroid weaning as described (if the patient is receiving steroids). At each visit, the investigator will calculate the average score for each symptom being collected on the diary (that is, the average of the daily scores since the previous visit, correcting for any day for which diary scores were not recorded). The investigator 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. An average diary score $\geq$0.5 (CANDLE or AGS diary) or $\geq$1.0 (JDM or SAVI diary) will be indicative of a lack of complete response and will trigger a dose escalation. An average diary score <0.5 (CANDLE or AGS

diary) or <1.0 (JDM or SAVI diary) will be indicative of a response to treatment and will trigger initiation of steroid weaning (if the patient is receiving steroids). The investigator should review the entire diary and diary score at each appropriate interval. If there is a trend in the diary scores, (that is, initial high scores resolve by the end of the diary period), the investigator has the option of escalating or not escalating the patient's dose of baricitinib.

Patients whose average diary scores decrease after receiving the maximum allowable dose level of baricitinib (as defined in the clinical protocol I4V-MC-JAGA(r)), but do not meet the threshold for steroid weaning (for patients receiving steroids at baseline), or an adequate response (do not reach an average daily CANDLE or AGS diary score <0.5 or a JDM or SAVI diary score <1.0), may continue in the study if the investigator determines that it is in the best interest of the patient to continue treatment. This will not be considered to be a protocol violation.

7.2. Discussion of Design and Control

This compassionate use study is an open-label, single-arm design intended to provide baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, severe JDM, or AGS. Baricitinib has not been investigated in children; therefore, patients will receive an initial dose that may be escalated using dose escalation tables to an effective and tolerable dose. The dose-escalation period allows for safety assessments in between dose escalations. This study, by the nature of compassionate use, is not intended to answer any research hypothesis; however, it is intended to provide a potential treatment for inflammatory conditions proven resistant to other therapies. Though the open-label, single-arm design has potential for the introduction of bias, the study design represents an ethical approach for treatment of these conditions within a compassionate use framework.

8. Study Population

Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder such as CANDLE syndrome, CANDLE-related syndrome, SAVI, or AGS, or will have been diagnosed with severe JDM. CANDLE syndrome clinically presents 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). Failure to thrive and lymphadenopathy and hypochromic or normocytic anemia can be seen (Ramot et al. 2010; Torrelo et al. 2010).

8.1. Inclusion Criteria

2) Have an average daily diary score of ≥0.5 (CANDLE or AGS diary) or ≥1.0 (SAVI or JDM diary) assessed over at least 2 weeks prior to entry, if available. Otherwise, patients can complete the diary after study consent is signed during the screening period and meet the inclusion criteria for enrollment into the study.

3) Are ≥17.5 months of age (or are ≥6 months of age with AGS). Patients younger than 17.5 months (or 6 months with AGS) of age can be considered for enrollment after discussion with the Sponsor.

5) Have been previously treated with at least 1 biologic therapy and, in the opinion of the investigator, did not respond or are no longer responding to therapy. If the patient has been diagnosed with CANDLE, Nakajo-Nishimura syndrome, SAVI, AGS, or an equivalent syndrome, the need for previous biologic therapy is not required.

6) Require treatment with oral corticosteroids (≥0.15 mg/kg/d of prednisone or its equivalent) for control of systemic signs and symptoms of their chronic inflammatory disease for at least 2 weeks prior to study entry, or in the opinion of the investigator, have failed an adequate course of steroids. Treatment with or failure of treatment with steroids is not required for patients with AGS.

8.1.3. Patients with Aicardi-Goutières Syndrome

Patients with AGS are eligible for entry into the study (that is, eligible to sign consent) only if they meet all of the common inclusion criteria (1 through 8 in Section 8.1 of the Clinical Protocol I4V-MC-JAGA(r)) and the following criterion:

48) A molecular diagnosis of AGS or neuroimaging and clinical findings consistent with a diagnosis of AGS.

8.3. Enrollment Criteria

8.3.1. Inclusion Criteria

29) Have a mean daily diary score of ≥0.5 (CANDLE or AGS diary) or ≥1.0 (SAVI or JDM diary) assessed over at least 2 weeks prior to enrollment, including patients who completed the diary after consent was signed.

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

10.2.2.2. 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 (Protocol Attachment 1, Study Schedule).

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

10.4. Appropriateness of Measurements

The use of the CANDLE, SAVI, or JDM diary score as a measure of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in autoinflammatory conditions conducted by investigators at the National Institutes of Health. The use of the AGS diary is based on precedent from patients treated by investigators at the Children's National Medical Center, Washington, DC.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Because this study of baricitinib is designed for compassionate use and the conditions being treated are rare, it is anticipated that only a few patients will be enrolled. The data are planned to be summarized with no formal statistical analyses. A formal sample size justification is, therefore, not needed. Sixty patients are expected to be enrolled.

14. References

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

Attachment 1. Protocol Addendum JAGA(3.1) Patient Daily Diary for AGS

Disease Activity Rating Scale				
Symptom	**Rating (Circle one)**			
Neurologic Disability	0	5	7	10
0 = Able to perform all activities of daily living independently with no restriction 5 = Able to participate in the following with some level of disability: ambulation, communication or fine motor tasks 7 = Requires functional or equipment support for any of the following: ambulation, communication or fine motor tasks 10 = Dependent for all activities of daily living and unable to ambulate, communicate or perform fine motor tasks even with support				
Crying	0	1	2	3
0 = No crying 2 = Inconsolable >2 minutes OR cry intermittently for <10 minutes 3 = Inconsolable >2 minutes AND cry intermittently for >10 minutes				
Length of Uninterrupted Sleep	0	1	2	3
0 = Sleeps more than 3 hours for infants< less than 6 months; more than 6 hours for children over 6 months 1 = Sleeps 2–3 hours at a time for infants less than 6 months; more than 4-5 hours for children over 6 months 2 = Sleeps 1–2 hours for infants less than 6 months,; more than 2-3 hours for children over 6 months 3 = Sleeps <1 hour for infants less than 6 months; greater than 1-2 hours for children over 6 months				
Generalized Seizure	0		8	
0 = No seizures 8 = Tonic-clonic, subtle staring, chewing, arching				
Fever	0		1	
0 = No fever 1 = Temp greater than or equal to 37.3°C (99.1°F)				
Excessive Irritability	0	1	2	3
1 = Consoling calms infant in 3–5 minutes 2 = Consoling calms infant in 6–15 minutes 3 = Consoling calms in >15 minutes or not at all				
Skin Findings body	0	1	2	3
0 = No rashes 1 = Blotchy red rash which comes and goes 2 = Persistently red spots which stay 3 = Persistent spots which do not blanche when pressed on				
Skin Findings hands, feet and ears	0	1	2	3
0 = No rashes 1 = Blotchy red rash which comes and goes 2 = Persistently red spots which stay 3 = Persistent spots which do not blanche when pressed on				

Attachment 2. Protocol Addendum Revisions

Overview

Protocol Addendum I4V-MC-JAGA(3) "Compassionate Use Treatment Protocol I4V-MC-JAGA(r): Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis" has been revised. The revised protocol addendum is indicated by revision 3.1 and will be used in place of any preceding version of this protocol addendum.

The overall changes and rationale for the changes made to this protocol addendum are as follows:

- The addendum is being revised in order to allow for an additional safety procedure (fundoscopy) to be completed as part of the physical examination if, in the opinion of the investigator, it is needed to monitor safety in specific AGS patients.
- Minor editorial changes were also made.

Revised Protocol Addendum

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

Section 3. Rationale for Addendum

This addendum applies to sites enrolling patients with Aicardi-Goutières Syndrome (AGS). AGS is a monogenic disorder resulting from loss of function 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). Given that AGS is an interferon-mediated disease, patients with AGS are expected to benefit from JAK1 and JAK2 inhibition and, thus, it may be beneficial to treat them with baricitinib. The purpose of this addendum is to add specific entry and patient assessment criteria for patients with AGS to the existing Protocol I4V-MC-JAGA(r). The addendum is being revised in order to allow for an additional safety procedure (fundoscopy) to be completed as part of the physical examination if, in the opinion of the investigator, it is needed to monitor safety in specific AGS patients.

Section 4. Protocol Additions

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

10.2.2.2. 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 (Protocol Attachment 1, Study Schedule).

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

10.4. Appropriateness of Measurements

The use of the CANDLE, SAVI, or JDM diary score as a measure of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in autoinflammatory conditions conducted by investigators at the National Institutes of Health. The use of the AGS diary is based on precedent from patients treated by investigators at the Children's National ~~Hospital~~Medical Center, Washington, DC.

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Approver: PPD
Approval Date & Time: 09-Sep-2016 14:52:40 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 09-Sep-2016 14:59:44 GMT
Signature meaning: Approved

Summary of changes for: Statistical Analysis Plan: Compassionate Use Treatment Protocol I4V-MC-JAGA

The primary purpose of this Supplemental SAP is to describe the handling of the additional data collected outside of the JAGA protocol. This includes efficacy evaluations beyond demographic and diary data.

Summary of relevant changes to SAP or Supplementary SAP regarding AGS-cohort

- Addition of AGS to the analysis plan with AGS-relevant supplemental clinical efficacy endpoints (Table 1)
- In the AGS population, the daily diary score will be the daily sum of the symptom scores for the AGS diaries, the daily diary score will remain the average of the daily symptom scores for the CANDLE and SAVI diaries.
- Analysis Neurologic trajectories (prior history of neurologic development compared to on study)

Table 1 Supplemental Clinical Efficacy Endpoints

Clinical Variable	Measures	JAGA Patient Population
AGS; collected under NCT03047369		
AGS scale scores	Assesses the achievement of pre-defined developmental milestones	CHOP
Skin and vascular manifestations	Symptom-specific daily diary scores as measured in JAGA; incidence of specific manifestations; photographs and case notes	CHOP
Biomarkers	ISG	CHOP
Patient, Parent, or Physician Reported Outcomes	Gross Motor Function Measure-88, Peabody Fine Motor Scale, Vineland Adaptive Behavior Scales	CHOP

Abbreviations: AGS = Aicardi-Goutières Syndrome, ISG = interferon regulatory gene expression scores

1. Statistical Analysis Plan: Compassionate Use Treatment I4V-MC-JAGA: Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Baricitinib (LY3009104)

Study I4V-MC-JAGA is an open-label compassionate use treatment program to provide baricitinib to patients with conditions expected to benefit from JAK inhibition: CANDLE, CANDLE-related conditions, SAVI, and severe juvenile dermatomyositis. Patients will receive an intial dose based on their weight class and disease type that may be escalated to determine a tolerable dose. Patients may be dosed for up to 288 weeks. It is anticipated that up to 35 patients may be treated with baricitinib in an individualized manner. The treatment guidelines contained herein are for compassionate use only. With in these guidelines, open-label baricitinib will only be administered to patients who meet inclusion and exclusion criteria.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I4V-MC-JAGA

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on 29 April 2016.

Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 02-May-2019 GMT

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3. Revision History

The I4V-MC-JAGA (JAGA) program is an open-label expanded access/compassionate use treatment program. While an SAP is out of scope for such programs as JAGA, the development of an SAP was undertaken in order to document planned handling of data from Study JAGA to support a regulatory submission. Study JAGA SAP Version 1 was approved 29 April 2016 prior to the interim database lock intended to support a regulatory submission (type B briefing document).

Study JAGA SAP Version 2 was approved prior to the interim database lock intended to support the supplemental New Drug Application submission. In addition to incorporating the changes made to the protocol amendment and the protocol addendum, the following were added to the SAP:

- Age categories for the patient characteristics
- Summaries of height and weight at endpoint
- Details of the analysis of change from baseline
- A listing of the methods of baricitinib administration
- A listing of the BK virus results.

4. Study Objectives

4.1. Primary Objective

The primary objective is to determine if the administration of baricitinib to patients with Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE), CANDLE-related conditions, Stimulator of Interferon Genes (STING)-Associated Vasculopathy with Onset during Infancy (SAVI), Juvenile Dermatomyositis (JDM) or Aicardi-Goutières Syndrome (AGS) results in reduction in the patient's mean daily diary scores as follows:

- CANDLE diary: reduction in mean daily score to <0.5
- SAVI diary: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and respiratory/breathing symptoms score <1.0 increase from baseline
- JDM diary: reduction in mean daily score exclusive of fever and headache symptoms by ≥0.25
- AGS diary: reduction in mean daily score to <0.5.

4.2. Secondary Objectives

The secondary objectives of the study are:

- to determine, in patients receiving steroids at baseline, if administration of baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, or AGS results 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, in patients receiving steroids at baseline, if the administration of baricitinib to patients with severe JDM results in a decrease in the daily dose of corticosteroids (systemic corticosteroids <0.2 mg/kg/day oral prednisone or a decrease of at least 25% of the patient's daily dose at baseline).
- to determine if the administration of baricitinib to patients with severe JDM results in a reduction in the patient's mean diary score exclusive of fever and headache symptoms to <1.0
- to determine if the administration of baricitinib to patients with AGS results in a reduction in the patient's mean diary score exclusive of neurological symptoms to <0.5.

5. Study Design

5.1. Summary of Study Design

Study JAGA is an open-label compassionate use treatment program for patients who weigh at least 8.5 kg and are at least 17.5 months of age (patients who weigh less than 8.5 kg or are younger than 17.5 months may be considered for enrollment after discussion with the Sponsor). Patients will receive an initial dose based on weight class and estimated glomerular filtration rate (eGFR). The dose may be escalated to determine a tolerable level. The patient's disease severity will be recorded by the patient or caregiver in a patient daily diary 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 steroids), as appropriate.

Figure JAGA.5.1 illustrates the study design.

5.2. Determination of Sample Size

Because this study of baricitinib is designed for compassionate use and the conditions being treated are rare, there is no minimum or maximum requirement of the number of patients to be studied.

5.3. Method of Assignment to Treatment

The study is an open-label trial with no randomization. All patients participating in this study will receive baricitinib.

5.3.1. Treatment Administered

All eligible patients will receive treatment with baricitinib as a twice-daily dose or multiple divided doses (as described in Protocol Section 7.1). Patients will receive an initial dose based on their weight class and eGFR and may have their dose escalated to determine a tolerable dose. Dose escalation will be performed up to the maximum allowable dose level, as long as there are no safety concerns that would preclude increasing the dose.

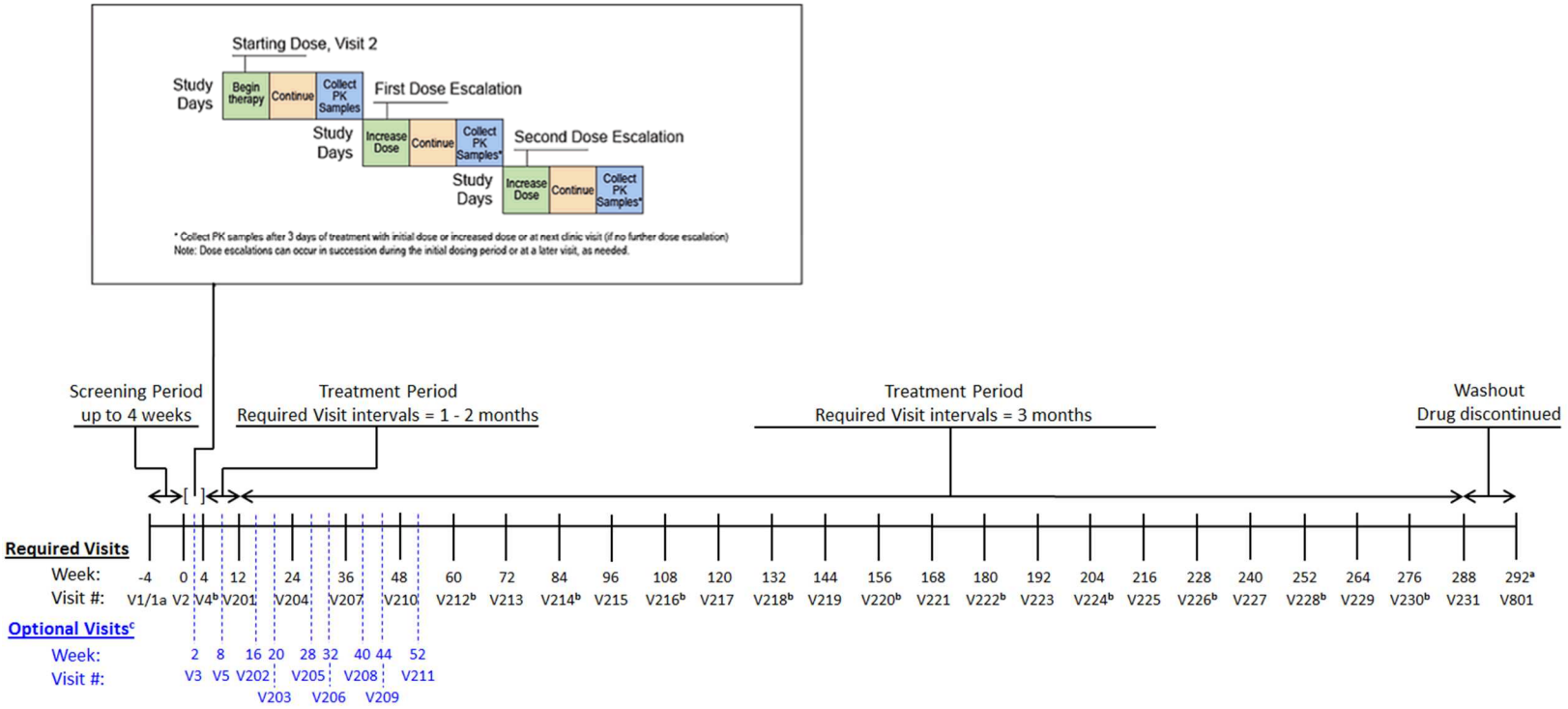

Figure JAGA.5.1. Clinical Protocol I4V-MC-JAGA study design.

Abbreviations: PI = principal investigator; PK = pharmacokinetics; V = visit.

a V801 (optional) should occur approximately 28 days after the last dose of investigational product.

b These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, laboratory samples should be obtained and tested locally, and a copy of the laboratory report sent to the PI.

c Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone

d Visit is performed, laboratory samples should be obtained and tested locally, and a copy of the laboratory report sent to the PI.

6. A Priori Statistical Methods

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

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly).

6.1. General Considerations

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Because the medical conditions being treated in this study are rare, it is anticipated that relatively few patients will be enrolled. Due to variable visit windows between patients, summaries by visit will not be provided. Therefore, data listings will be the primary tool used to summarize the results from this study with additional summary statistics (as appropriate).

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

When summary statistics are deemed appropriate, continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. When summary statistics are deemed appropriate, categorical data will be summarized as frequency counts and percentages.

The endpoint will be considered the last non-missing assessment while on study drug. Week will be calculated as the number of weeks after the first dose of baricitinib.

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

6.1.1. Definition of Baseline and Postbaseline Measures

The treatment period starts after administration of the first dose of baricitinib at Visit 2 (Week 0) and ends on the date of the final visit in the treatment period or the early discontinuation visit. The endpoint will be the last non-missing postbaseline measurement during the treatment period.

Baseline of the treatment period will be defined as the last available value on or before the first dose of baricitinib. In most cases, this will be the measure recorded at Week 0 (Visit 2).

Change from baseline will be calculated as the visit value of interest minus the baseline value.

Any measurement collected after the first dose of baricitinib will be considered a postbaseline measurement.

Baseline of the washout period is defined as the date of the final visit or early termination in the treatment period. Endpoint of the washout period is Visit 801.

6.2. Handling of Dropouts or Missing Data

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

6.3. Use of an "Efficacy Subset" of Patients

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

Enrolled population set includes all patients who have entered the study and who are not considered screen fails at Visit 2 (i.e. patients not excluded due to not meeting inclusion criteria or meeting exclusion criteria at Visit 2).

Safety population set includes all enrolled patients who receive at least 1 dose of baricitinib and who did not discontinue the study for the reason "Lost to Follow-up" at the first postbaseline visit (Visit 3).

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

6.4. Patient Disposition

The following patient disposition summaries will be provided:

- Frequency counts and percentages of patients who were screen fails (excluded at Visit 2 prior to receiving baricitinib) will be provided.
- Frequency counts and percentages of patients who complete or discontinue early from the study will be summarized separately by disease diagnosis along with their reason for study discontinuation.
    - Among patients who completed the study, frequency counts and percentages of patients who completed the safety closeout visit, or did not complete the safety closeout visit will be presented by disease diagnosis.
    - Among patients who discontinued early from the study, frequency counts and percentages of patients who completed the safety closeout visit or did not complete the safety closeout visit will be presented by disease diagnosis.

A listing of patient disposition during the treatment period will be provided for all enrolled patients who have completed or discontinued from the treatment period, with the date of enrollment, the duration of their participation in the study (days and years), last completed visit, date of last completed visit, the primary reason for study discontinuation, and additional details that support the reason for discontinuation. If the reason for discontinuation is an adverse event (AE), then the preferred term will be specified. If the reason for discontinuation is death, the date of death and related AE or other reason for death will be specified. A separate disposition listing will be provided for patients who entered the washout period.

A by-patient listing of reason for screen failure including the visit that occurred will be provided. The number of patients who entered the study, enrolled in the study, and are included in the safety population will be summarized.

6.5. Patient Characteristics

Patient characteristics including demographics will be summarized by disease diagnosis. The following continuous demographic and baseline characteristic variables will be summarized using descriptive statistics.

- Age at the time of study entry (in years and separately in months).
- Height (cm)
- Weight (kg) (as recorded at Visit 2, unless missing, in which case the Visit 1 result will be used).

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

- Sex
- Weight categories (kg) (<10 , ≥10 - <20, ≥20 - <30, ≥30 - <40, ≥40 - <50, ≥50 - <60, and ≥60)
- Race
- Ethnicity
- Age categories (years) (<2, 2 to <12, 12 to <18 and ≥18).

Baseline is defined as in Section 6.1.1 unless otherwise specified.

A by-patient listing of demographic and baseline characteristics will be provided including age at study entry (years and months), body weight (kg), height (cm), body mass index (BMI), and BMI percentile. Height and weight at endpoint will also be summarized using descriptive statistics. Where data from at least 5 patients are available, the change from baseline at endpoint will be modeled using Analysis of Variance (ANOVA) with disease diagnosis as the factor, and the least-squares means (LSM), standard errors (SEs), p-values and 95% confidence intervals (CIs) will be presented. The analysis will be repeated by age group. A by-patient listing of demographic and other characteristics at endpoint will be provided with duration on study (years), age, weight, height, BMI, and BMI percentile.

6.6. Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary. Medication start and stop dates will be compared to the date of the first dose of study treatment (recorded on the Study Drug Administration page of the electronic case [clinical] report form [eCRF]) to allow medications to be classified as ‘prior’ or ‘concomitant’.

Medications that start and end before the first dose date will be classified as ‘prior’ medications. Medications that end on or after the first dose date will be classified as ‘concomitant’

medications. Note that medications with partial or missing start and/or stop dates will be assumed to be 'concomitant' unless there is evidence, through comparison of partial dates, to suggest otherwise.

A by-patient listing of all non-steroid concomitant medications will be provided including therapy type (prior or concomitant), preferred term, reported term, start and end date, start and end week, a flag if the medication was started after the last dose of baricitinib, and indication. A separate by-patient listing of steroid concomitant medications will be provided including therapy type (prior or concomitant), preferred term, reported term, start and end date, start and end week, frequency, route, and a flag if the medication was started after the last dose of baricitinib.

Non-steroid and steroid concomitant medications will be summarized separately by preferred term and disease diagnosis.

6.7. Efficacy Analyses

Efficacy analyses will use the efficacy population defined in Section 6.3 .

6.7.1. Primary Analyses

The primary objective is to determine if the administration of baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, JDM, or AGS results in reduction in the patient's mean daily diary scores as follows:

- CANDLE diary: reduction in mean daily score to <0.5
- SAVI diary: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and respiratory/breathing symptoms score <1.0 increase from baseline
- JDM diary: reduction in mean daily score exclusive of fever and headache symptoms ≥0.25
- AGS diary: reduction in mean daily score to <0.5.

The calculated mean diary scores at baseline and at endpoint will be summarized using descriptive statistics. Where data from at least 5 patients are available, the change from baseline at endpoint will be modeled using ANOVA with disease diagnosis as the factor, and the LSM, SEs, p-values and 95% CIs will be presented. This analysis will be repeated for each symptom score. A by-visit listing of the calculated mean diary score (defined in Section 6.8), change in diary score, percent change in diary score, mean symptom scores, and change from baseline in each symptom score will be provided. The number and percentage of patients achieving a decrease in the appropriate diary score will be summarized using the listing.

6.7.2. Secondary Efficacy Analyses

The secondary objectives of the study are:

- to determine, in patients receiving steroids at baseline, if administration of baricitinib to patients with CANDLE, CANDLE-related conditions, SAVI, or AGS results 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, in patients receiving steroids at baseline, if the administration of baricitinib to patients with severe JDM results in a decrease in the daily dose of corticosteroids (systemic corticosteroids <0.2 mg/kg/day oral prednisone or a decrease of at least 25% of the patient's daily dose at baseline).
- to determine if the administration of baricitinib to patients with severe JDM results in a reduction in the patient's mean diary score exclusive of fever and headache symptoms to <1.0
- to determine if the administration of baricitinib to patients with AGS results in a reduction in the patient's mean diary score exclusive of neurological symptoms to <0.5.

The total daily corticosteroid dose (mg), corticosteroid dose per weight (mg/kg), change from baseline, and percent change from baseline of corticosteroid doses will be listed. The number and percentage of patients achieving a reduction in corticosteroid dose will be summarized.

6.7.3. Additional Analyses of the Primary Outcome

Additional summaries (where applicable) and listings by patient sub-populations (eg. age, sex) may be created as appropriate.

6.8. Patient Diary and Diary Score

The CANDLE and CANDLE-Related Diary is a daily assessment of disease severity completed by the patient (if able), parent/caregiver, or healthcare provider/medical staff. The diary assesses 5 prominent disease symptoms (fever, rash, musculoskeletal pain, headache, and fatigue) with each symptom scored on a 5-point numeric rating scale ranging from 0 (no symptom) to 4 (severe symptom) as shown below in Table JAGA.6.1. The respondent writes in the value that best corresponds to the severity of the symptom on that day.

Table JAGA.6.1. CANDLE and CANDLE-Related Diary Scores

0 = No fever	0 = No rash	0 = No pain	0 = No headache	0 = No fatigue
1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild headache not requiring medication or any adjustments of daily activities	1 = Mild fatigue, no functional impact
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	2 = Rash covering 10% of body surface area	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Headache requiring medication or having mild functional impact	2 = Moderate fatigue with mild functional impact
3 = Fever requiring medication with significant impact on daily activities (missing school, listlesness)	3 = Rash covering more than 30% of body surface area	3 = Pain requiring medication or having a severe functional impact	3 = Headache requiring medication and having a severe functional impact	3 = Severe fatigue with a severe functional impact
4 = Fever forcing the patient to be bedridden	4 = Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	4 = Severe fatigue resulting in patient staying in bed most of the time

Abbreviation: CANDLE = Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature.

The SAVI Diary is a daily assessment of disease severity completed by the patient (if able), parent/caregiver, or healthcare provider/medical staff. The diary assesses 6 prominent disease symptoms (fever, rash, musculoskeletal pain, fatigue, respiratory/breathing symptoms, and ulcers/ischemic lesions) with each symptom scored on a 5-point numeric rating scale ranging from 0 (no symptom) to 4 (severe symptom) as shown below in Table JAGA.6.2. The respondent writes in the value that best corresponds to the severity of the symptom on that day.

Table JAGA.6.2. SAVI Diary Scores

0 = No fever	0 = No rash	0 = No pain	0 = No fatigue	0 = No breathing problems	0 = No ulcers
1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild fatigue, no functional impact	1 = Mild breathing problems / rapid breathing / coughing, no functional impact	1 = Few ulcers, only in 1 location and/or no drainage, no ischemia
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	2 = Rash covering 10% of body surface area	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Moderate fatigue with mild functional impact	2 = Moderate breathing problems / rapid breathing / coughing with mild functional impact	2 = Ulcers in more than 1 location and/or with some drainage, no ischemia
3 = Fever requiring medication with significant impact on daily activities (missing school, listlesness)	3 = Rash covering more than 30% of body surface area	3 = Pain requiring medication or having a severe functional impact	3 = Severe fatigue with a severe functional impact	3 = Severe breathing problems / rapid breathing / coughing with a severe functional impact	3 = Ulcers in multiple locations and/or significant drainage, and/or any ischemia
4 = Fever forcing the patient to be bedridden	4 = Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe fatigue resulting in patient staying in bed most of the time	4 = Severe breathing problems / rapid breathing / coughing which result in patient staying in bed most of the time	4 = Severe ulcers / ischemic lesions in multiple locations

Abbreviation: SAVI = Stimulator of Interferon Genes (STING)-Associated Vasculopathy with Onset during Infancy.

The JDM Diary is a daily assessment of disease severity completed by the patient (if able), parent/caregiver, or healthcare provider/medical staff. The diary assesses 6 prominent disease symptoms (fever, rash, musculoskeletal pain, headache, fatigue, and weakness) with each symptom scored on a 5-point numeric rating scale ranging from 0 (no symptom) to 4 (severe symptom) as shown below in Table JAGA.6.3. The respondent writes in the value that best corresponds to the severity of the symptom on that day.

Table JAGA.6.3. JDM Diary Scores

0 = No fever	**0** = No rash	**0** = No pain	**0** = No headache	**0** = No fatigue	0 = No muscle
1 = Fever without impact on daily activity	**1** = Rash barely present	**1** = Mild pain not requiring medication, no limping	**1** = Mild headache not requiring medication or any adjustments of daily activities	**1** = Mild fatigue, no functional impact	1 = Mild weakness
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	**2** = Rash generally brighter pink to red	**2** = Pain requiring medication or leading to limping or other mild functional impact	**2** = Headache requiring medication or having mild functional impact	**2** = Moderate fatigue with mild functional impact	2 = Moderate weakness
3 = Fever requiring medication with significant impact on daily activities (missing school, listlesness)	**3** = Rash generally bright red	**3** = Pain requiring medication or having a severe functional impact	**3** = Headache requiring medication and having a severe functional impact	**3** = Severe fatigue with a severe functional impact	3 = Severe weakness
4 = Fever forcing the patient to be bedridden	**4** = Worst rash ever	**4** = Severe pain, child refusing to walk, or staying in bed most of the time	**4** = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	**4** = Severe fatigue resulting in patient staying in bed most of the time	4 = Extremely severe weakness

Abbreviation: JDM = juvenile dermatomyositis.

The AGS Diary is a daily assessment of disease severity completed by the patient (if able), parent/caregiver, or healthcare provider/medical staff. The diary assesses 8 prominent disease symptoms (fever, neurologic disability, crying, length of uninterrupted sleep, generalized seizure, excessive irritability, skin findings on body and skin findings on hands, feet and ears). The scoring for each symptom is shown below in Table JAGA.6.4. The respondent writes in the value that best corresponds to the severity of the symptom on that day.

Table JAGA.6.4. AGS Diary Scores

0 = Able to perform all activities of daily living independently with no restriction.	**0** = No crying	**0** = sleeps more than 3 hours for infants less than 6 months; more than 6 hours for children over 6 months			**0** = No Irritability	**0** = No rashes	**0** = No rashes
5 = Able to participate in the following with some level of disability: ambulation, communication or fine motor tasks	**1** = inconsolable >2 minutes **OR** cry intermittently for <10 minutes"	**1** = sleeps 2-3 hours at a time for infants less than 6 months; more than 4-5 hours for children over 6 months			**1** = Consoling calms infant in 3-5 minutes	**1** = Blotchy red rash which comes and goes	**1** = Blotchy red rash which comes and goes
7 = Requires functional or equipment support for any of the following: ambulation, communication or fine mortor tasks	**2** = inconsolable >2 minutes **AND** cry intermittently for >10 minutes	**2** = sleeps 1-2 hours for infants less than 6 months; more than 2-3 hours for children over 6 months	**0** = No seizures	**0** = No fever	**2** = Consoling calms infant in 6-15 minutes	**2** = Persistently red spots which stay	**2** = Persistently red spots which stay
10 = Dependent for all activities of daily living and unable to ambulate, communicate or perform fine motor tasks even with support	**3** = Inconsolable for > 10 minutes	**3** = sleeps <1 hour for infants less than 6 months; greater than 1-2 hours for children over 6 months	**8** = Tonic-clonic, subtle staring, chewing, arching	**1** = Temperature greater than or equal to 37.3°C (99.1°F)	**3** = Consoling calms in more than 15 min or not at all	**3** = Persistent spots which do not blanche when pressed	**3** = Persistent spots which do not blanche when pressed
Neurologic Disability	**Crying**	**Length of Uninterrupted Sleep**	**Generalized Seizure**	**Fever**	**Excessive Irritability**	**Skin Findings on Body**	**Skin Findings, hands, feet, and ears**

Abbreviation: AGS = Aicardi-Goutières Syndrome.

At each visit, the investigator calculates the average score for each symptom being collected on the diary (that is, the average of the daily scores since the previous visit, correcting for any day for which diary scores were not recorded). The average diary score assessed over at least 2 weeks prior to entry, if available, will be used for Visit 1. Otherwise, patients can complete the diary after study consent is signed for at least a 2-week timeframe during the screening period and meet the inclusion criteria for enrollment into the study at Visit 2. The investigator 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. Only the average symptom scores at each visit (calculated by the investigator/site personnel) and the mean diary score at each visit (calculated by the investigator/site personnel) are entered into the JAGA database. The average diary score at each visit will be re-calculated based on the average symptom scores at each visit that were entered in the JAGA database. Additionally, the average diary score for SAVI patients will be calculated as the average of the symptom scores excluding the respiratory/breathing symptom score, excluding fever and headache symptoms for JDM patients and excluding neurological symptoms for AGS patients. If more than 50% symptom scores are missing for the specified calculation then the average diary score will not be calculated.

No formal psychometric validation (per the Food and Drug Administration [FDA] patient-reported outcome [PRO] guidance) has been completed for the diary given the rarity of CANDLE Syndrome and the resulting small number of patients assessed using the diary. However, similar types of diaries have been used to study conditions such as neonatal-onset multisystem inflammatory disease (NOMID) and have supported associated label updates (anakinra [Kineret®]; [Goldbach-Mansky et al. 2006]). The cut-off for determining response (<0.5 and <1.0 for CANDLE/CANDLE-Related and SAVI patients, respectively) were based on investigator judgment based on previous experience with NOMID patients. The same cut-offs were used in NOMID patients.

6.9. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

This will be described in a separate Population Pharmacokinetic Analysis Plan.

6.10. Safety Analyses

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

6.10.1. Extent of Exposure

A by-patient listing will be created including the visit, week, patient's weight, total daily dose, total daily dose per weight (mg/kg), dose frequency, the treatment start date or dose adjustment date, dose adjustment type (increase, decrease, omitted, and treatment schedule changed), and reason dose adjusted.

Baricitinib exposure will be summarized including frequency counts and percentages of patients who have taken baricitinib in subset of months (>0-6, >6-12, >12-18, >18-24, >24-30, >30-36, >36-42, >42-48, >48-54, >54-60, and >60 months), duration of exposure to baricitinib (in months and separately in years), and the patient years of exposure (PYE) will be summarized. PYE is defined as the sum of all patient exposure time in years for the specific disease diagnosis. A by-patient listing of study drug exposure will be provided including duration of exposure in years and separately in weeks. Duration in days of baricitinib exposure is defined as the date of last dose of baricitinib minus the date of first dose of baricitinib +1. A by-patient listing of any additional descriptions of the method of baricitinib administration will also be created.

6.10.2. Adverse Events

Adverse events are classified based upon the Medical Dictionary for Regulatory Activities (MedDRA). Each AE will be coded to system organ class (SOC) and Preferred Term (PT) using the MedDRA version that is current at the time of database lock. Severity of AEs is recorded as mild, moderate, or severe. Adverse events will use the safety population defined in Section 6.6.

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

same SOC and PT. For events that are sex-specific, the denominator and computation of the percentage will include only patients from the given sex.

Exposure adjusted incidence rate (EAIR) is expressed as the number of patients reporting an adverse event per 100 PYE to treatment and is derived as 100 times the incidence of the event divided by the sum of all patient exposure time (in years for the specific disease diagnosis).

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

6.10.2.1. Adverse Events

An overview of AEs including deaths, SAEs, TEAEs, and patients discontinued from study due to an AE will be summarized for the treatment period. An overview of AEs including deaths, SAEs, discontinuation-emergent adverse events (DEAE), and patients discontinued from study due to an AE will be summarized for the washout period. A by-patient listing of all AEs will be provided.

Pre-existing conditions are defined as any physical complaints/symptoms (AEs) that present prior to initiation of treatment with baricitinib and do not worsen in severity after starting baricitinib treatment. The frequency and percentage of patients who reported a pre-existing condition will be summarized by disease diagnosis using PT nested within SOC.

6.10.2.2. Serious Adverse Events

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

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

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The number and percentage of patients who reported any SAE will be summarized by disease diagnosis using PT nested within SOC, including the PYE and EAIR, for the treatment period and for the washout period, separately. A by-patient listing of all SAEs will be provided.

6.10.2.3. Treatment-emergent Adverse Events

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

Treatment-emergent AEs will be summarized by MedDRA PT nested within cluster with clusters ordered alphabetically, and events ordered within each cluster by decreasing frequency, including the PYE and the EAIR. Clusters will be groups of preferred terms that the medical team determines are linked or similar.

6.10.2.4. Discontinuation-Emergent Adverse Events

Adverse events will be considered DEAEs if the AEs begin or increase in severity after the last visit during the treatment period. If the maximum severity during the washout period is greater than the treatment period severity, the event is considered to be discontinuation-emergent. Discontinuation-emergent AEs will be summarized by SOC and PT.

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

6.10.3.1. Adverse Events of Special Interest

Adverse events of special interest include the following:

- Infections
- myelosuppressive events
    - anemia (hemoglobin <6.5 g/dL),
    - leukopenia (White blood cell [WBC] count <2000 cells/µL),
    - neutropenia (absolute neutrophil count [ANC] <1000 cells/µL),
    - lymphopenia (lymphocyte count <500 cells/µL), and
    - thrombocytopenia (platelet count <75,000/µL)
- thrombocytosis (platelet count >600,000/µL)
- elevations in alanine transaminase (ALT) or aspartate aminotransferase (AST) (>3 times upper limit of normal [ULN]) with total bilirubin (>2 times ULN).

Treatment-emergent infection AESIs will be summarized by disease diagnosis, including the PYE and the EAIR, using PT nested within the SOC of infections and infestations. Infection AESIs will be provided in a listing.

Adverse events of special interest based on laboratory data and according to the definitions listed above will be summarized. A by-patient listing of laboratory results at all visits for the laboratory analyte associated with a specific AESI (anemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia, thrombocytosis, or abnormal ALT or AST with elevated bilirubin) will be created.

6.10.4. Clinical Laboratory Evaluation

Hematology, chemistry, urinalysis, fasting lipids and BK virus laboratory measurements will be analyzed by local laboratories, and will be collected in the conventional (CN) units that the local laboratory uses to measure each analyte. The CN units will require conversion to standardized Système International (SI) units for analysis purposes. Hematology, chemistry, urinalysis, and fasting lipids laboratory parameters at baseline and at endpoint will be summarized using descriptive statistics. Where data from at least 5 patients are available, the change from baseline at endpoint will be modeled using ANOVA and the LSM, SEs, p-values and 95% CIs will be presented. Observed values (CN and SI) for hematology, chemistry, urinalysis, and fasting lipids laboratory parameters will be listed separately for each patient, including visit, week of visit, values, units, reference ranges, and flag for low/high results. BK virus results in the blood and urine will also be listed separately for each patient, including age at collection, visit, week of visit, values and units.

The frequency count and percentage of patients with treatment-emergent hepatic laboratory abnormalities at any time postbaseline will be summarized for patients at risk (those with normal baseline values with respect to the direction of the abnormality of interest and have at least one postbaseline measure).

Abnormal elevations in ALT and AST will be summarized as follows:

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

6.10.5. Vital Signs and Other Physical Findings

Graphical displays of individual patient data for pulse, systolic blood pressure, diastolic blood pressure, and weight over time with associated tables of values and changes from baseline will be created.

6.11. Protocol Violations

Protocol deviations will be tracked by the clinical team, and the following categories of important protocol deviations will be reported:

- inclusion/exclusion deviations,
- improper administration of the informed consent,
- prohibited medication,
- protocol non-compliance,
- missing procedures,
- and study drug administration and compliance deviations

A summary of the number and percentage of patients with an important protocol deviation by disease diagnosis and by type of deviation will be provided. A listing of important protocol deviations will be provided with any additional details.

6.12. Interim Analyses and Data Monitoring

An interim analysis is planned to support regulatory submission of the Study JAGA data. Adjustment to type I error is not applicable as Study JAGA is a single arm, open-label program.

6.13. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements. Analyses provided for the CTR requirements include the following: A summary of AEs will be provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients in the treatment group may not be included if a 5% threshold is chosen.

7. References

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.

8. Appendices

Appendix 1. Protocol I4V-MC-JAGA Study Schedule

Study Schedule, Protocol I4V-MC-JAGA

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4**[q]		**201**	**204, 207, 210**	**212**[q]**, 213, 214**[q]**, 215, 216**[q]**, 217, 218**[q]**, 219, 220**[q]**, 221, 222**[q]**, 223, 224**[q]**, 225, 226**[q]**, 227, 228**[q]**, 229, 230**[q]**, 231**	**ET**[a]	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52**[b]	**60 to 288**[c]	**–**	**292**
Number of days at visit		**28 to 2**		**Variable**[d]	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Informed consent		X										
Demographic characteristics		X										
Height		X		X	X	X	X	X	X	X	X	X
Weight		X		X	X	X	X	X	X	X	X	X
Administer tuberculosis test		X[f]										
Read tuberculosis test			X									
Chest x-ray		X[g]										
Electrocardiogram (ECG)		X										
Review inclusion/exclusion criteria		X										
Medical history		X										
Physical examination		X		X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X	X
Assessment of JDM core measures[h]		X										
Vital signs		X		X	X	X	X	X	X	X	X	X
Diary Scores		X		X[i]	X	X	X	X	X	X	X	X
Concomitant medications		X		X	X	X	X	X	X	X	X	X
Preexisting conditions		X										

(continued)

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4**[q]		**201**	**204, 207, 210**	**212**[q]**, 213, 214**[q]**, 215, 216**[q]**, 217, 218**[q]**, 219, 220**[q]**, 221, 222**[q]**, 223, 224**[q]**, 225, 226**[q]**, 227, 228**[q]**, 229, 230**[q]**, 231**	**ET**[a]	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**−4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52**[b]	**60 to 288**[c]	**–**	**292**
Number of days at visit		**28 to 2**		**Variable**[d]	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Adverse events				X	X	X	X	X	X	X	X	X
Investigational drug dose modifications				X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]		
Investigational product returned and compliance assessed					X	X	X	X	X	X		
Laboratory												
Hematology		X		X[l]	X	X	X	X	X	X	X	X
Serum chemistry		X		X[l]	X	X	X	X	X	X	X	X
Fasting lipid panel		X					X	X	X	X	X	X
Urinalysis		X		X[l]	X	X	X	X	X	X	X	X
HBsAg, HBcAb, HBsAb		X[m]										
Hepatitis C antibody		X[m]										
HIV		X[m]										
Thyroid stimulating hormone		X[f]										
BK virus quantitative PCR, plasma		X				X		X	X[t]	X[t]	X	X
BK virus quantitative PCR, urine		X				X		X	X[t]	X[t]	X	X

(continued)

Serum pregnancy test[n]	X										
Urine pregnancy test[n]			X	X	X	X	X	X	X	X	X
Plasma baricitinib concentration[o]			X	X	X	X	X	X	X		
Pulmonary function tests (SAVI patients only)[p]	X		X	X	X	X	X	X	X	X	X

Abbreviations: ET = early termination; JDM = juvenile dermatomyositis; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibiody; HBsAb = hepatitis B surface antibody; HIV = human immunodeficiency virus; SAVI = STING-associated vasculopathy with onset during infancy.

a Early termination visit is required if early termination occurs.

b Visits occur at approximately 4-week intervals during Weeks 16 through 52 (including both required and optional visits)

c Visits occur at approximately 12-week intervals during Weeks 60 through 288.

d Visit 2 encompasses the initial dosing period and can vary in time depending on whether the patient progresses through the first and second dose escalation during this period. Four days is the minimum time.

e Every effort should be made to schedule patient visits within the allowable visit window; however, if a patient visit is scheduled outside the visit window, it will not be considered a protocol violation.

f If results are available from testing within 1 month, then the patient will not have to be retested.

g If a chest x-ray has not been performed in the 6 months prior to screening visit.

h Juvenile dermatomyositis patients only.

i At least 2 consecutive weeks of diary scores are required prior to beginning investigational product.

j Each time study dose is adjusted during Visit 2, this eCRF will be completed.

k See dose escalation schedule (Table JAGA.7.1 of the Protocol). Each time study dose is adjusted, this eCRF will be completed. Samples for chemistry, hematology, and urinalysis may be collected 2 weeks after final dose increase. Collect pharmacokinetic samples as described in Section 10.3.2 of the Protocol.

l Collect prior to each dose escalation. Investigator will review to ensure dose escalation is appropriate.

m If results are available from testing within the previous 3 months, then the patient will not have to be retested.

n 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 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.

o Baricitinib concentration samples will be collected as described in Section 10.3.2 of the Protocol. Samples will be collected after Visit 2 if patient has a dose escalation (see Table JAGA 7.1 of the Protocol) or as needed for safety monitoring in patients with eGFR < 120 mL/min/1.73 m^2.

p Pulmonary function tests are required for SAVI patients only. Pulmonary function tests may include vital signs, pulse oximetry, imaging, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide. During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased.

q These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2 of the Protocol.

r Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained locally.

s Optional physical exams may be performed as needed to document clinically active disease, i.e. rash, fever, arthritis, worsening of splenomegaly, hepatomegaly, and corticosteroid side effects i.e. increase in abdominal girth, cataracts, vertebral fractures due to osteoporosis, Cushinhgoid habitus, substantial weight gain, avascular necrosis, dyslipidemia, hypertension, opportunistic infections or stunted growth, hirsutism, acanthosis nigricans and others.

t BK virus testing required only at on-site, required visits.

Appendix 2. Protocol I4V-MC-JAGA Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b,c]	**Serum Chemistry**[a,b]
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin[c]
Mean cell volume (MCV)	Direct bilirubin[c]
Mean cell hemoglobin concentration (MCHC)	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT/SGPT)[c]
Reticulocyte	Aspartate aminotransferase (AST/SGOT)[c]
Absolute counts of:	Blood urea nitrogen (BUN)[c]
Neutrophils, segmented	Creatinine[c]
Neutrophils, juvenile (bands)	Calcium
Lymphocytes	Glucose
Monocytes	Albumin
Eosinophils	Total protein
Basophils	Creatine phosphokinase (CPK)
Platelets	Uric acid
	Gamma glutamyl transferase (GGT)
	Aldolase[d]
Lipid[e]	
Total cholesterol (TC)	
Low-density lipoprotein (LDL)	
High-density lipoprotein (HDL)	**Other Tests**[a]
Triglycerides	Hepatitis B Surface antigen (HBsAg)[g]
	Anti-Hepatitis B Core antibody (HBcAb)[g]
Urinalysis[a,b,f]	Hepatitis B Surface antibody (HBsAb)[g]
	Hepatitis B Virus DNA[g]
Specific gravity	Human immunodeficiency virus (HIV)[g]
pH	Hepatitis C antibody[h]
Protein	Thyroid-stimulating hormone (TSH)[g]
Glucose	Thyroxine (T4)[g]
Ketones	Pregnancy Test[i]
Bilirubin	QuantiFERON®-TB Gold[g,j]
Urobilinogen	Baricitinib serum concentration
	BK virus quantitative PCR, plasma
	BK virus quantitative PCR, urine
	Urine cytology[f]
	eGFR
Blood	
Leukocyte esterase	
Nitrite	

Abbreviations: PPD = purified protein derivative; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis; WBC = white blood cells.

Footnotes on next page.

[a] Assayed by local clinical laboratory.
[b] Unscheduled blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator.
[c] If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2 of the Protocol.
[d] Perform if inflammatory myositis is present.
[e] Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to test.
[f] Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.
[g] Test required at Visit 1 only to determine eligibility of patient for the study.
[h] A positive hepatitis C antibody result will be confirmed with a positive hepatitis C virus result.
[i] For all women of childbearing potential, a serum pregnancy test will be performed at Visit 1 and a urine pregnancy test (local laboratory) will be performed at Visit 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
[j] The QuantiFERON®-TB Gold 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. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

Appendix 3. CANDLE/CANDLE-Related Diary, SAVI Diary, JDM and AGS Diary

CANDLE and CANDLE - Related Diary

Date of last clinic visit: _____ **Study #:** _____ **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column.

Total Daily Dose _____ **(mg)**

Dose breakdown _____ **(mg)**

Dose Frequency - circle or check one. (number of doses per day)

If your dose or dose frequency changes, start a new diary page starting with the current calendar day.

- 1 time per day ☐
- 2 times per day ☐
- 3 times per day ☐
- 4 times per day ☐
- 5 times per day ☐

0 = No fever	**0** = No rash	**0** = No pain	**0** = No headache	**0** = No fatigue
1 = Fever without impact on daily activity	**1** = Rash barely present	**1** = Mild pain not requiring medication, no limping	**1** = Mild headache not requiring medication or any adjustments of daily activities	**1** = Mild fatigue, no functional impact
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	**2** = Rash covering 10% of body surface area	**2** = Pain requiring medication or leading to limping or other mild functional impact	**2** = Headache requiring medication or having mild functional impact	**2** = Moderate fatigue with mild functional impact
3 = Fever requiring medication with significant impact on daily activities (missing school, listlessness)	**3** = Rash covering more than 30% of body surface area	**3** = Pain requiring medication or having a severe functional impact	**3** = Headache requiring medication and having a severe functional impact	**3** = Severe fatigue with a severe functional impact
4 = Fever forcing the patient to be bedridden	**4** = Worst rash ever or covering over 30% of body surface area or hurting or stinging	**4** = Severe pain, child refusing to walk, or staying in bed most of the time	**4** = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	**4** = Severe fatigue resulting in patient staying in bed most of the time

Day	Date MM/DD/YYYY	Total Daily Dose JAGA (mg) Given	Missed JAGA Dose (mg) & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Dose of Steriods (mg)	Name or initials of person entering information, each day
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
15											
16											
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25											
26											
27											
28											
29											
30											
31											

NIH Study Team

Reviewer Name: _____ Reviewer Signature: _____ Date Reviewed: _____

JDM Diary

Date of last clinic visit: _____ **Study #:** _____ **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column.

Total Daily Dose _____ **(mg)**

Dose breakdown _____ **(mg)**

Dose Frequency - circle or check one. (number of doses per day)

If your dose or dose frequency changes, start a new diary page starting with the current calendar day.

- 1 time per day ☐
- 2 times per day ☐
- 3 times per day ☐
- 4 times per day ☐
- 5 times per day ☐

0 - No fever	0 - No rash	0 - No pain	0 - No headache	0 - No fatigue	0 - No muscle
1 - Fever without impact on daily activity	1 - Rash barely present	1 - Mild pain not requiring medication, no limping	1 - Mild headache not requiring medication or any adjustments of daily activities	1 - Mild fatigue, no functional impact	1 - Mild weakness
2 - Fever requiring fever-reducing medication or with mild impact on daily	2 - Rash generally brighter pink to red	2 - Pain requiring medication or leading to limping or other mild functional	2 - Headache requiring medication or having mild functional impact	2 - Moderate fatigue with mild functional impact	2 - Moderate weakness
3 - Fever requiring medication with significant impact on daily activities (missing school	3 - Rash generally bright red	3 - Pain requiring medication or having a severe functional impact	3 - Headache requiring medication and having a severe functional impact	3 - Severe fatigue with a severe functional impact	3 - Severe weakness
4 - Fever forcing the patient to be bedridden	4 - Worst rash ever	4 - Severe pain, child refusing to walk, or staying in bed most of the time	4 - Severe headache resulting in patient staying in bed most of the day or lying down due to headache	4 - Severe fatigue resulting in patient staying in bed most of the time	4 - Extremely severe weakness

Day	Date MM/DD/YYYY	Total Daily Dose JAGA mg Given	Missed JAGA Dose & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Weakness	Dose of Steroids (mg)	Name or initials of person entering information, each day
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
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19												
20												
21												
22												
23												
24												
25												
26												
27												
28												
29												
30												
31												

Key for scoring per symptom:

Fever	0 - 4 listed above
Rash	0 - no rash
	1 - Faint pink - involvement of a smaller area, such as joints, eyelids, and/or cheeks
	2 - Pink to red - involvement of moderate area, such as joints, face, hands, and arms
	3 - Bright red - often with more extensive involvement of moderate area, such as joints, face, neck & shoulders, hands & arms, lower extremities, & possibly trunk or
	4 - Worst - Extremely bright red & often with itchiness, scratching, or with
Musculoskeletal	0 - 4 listed above
Headache	0 - 4 listed above
Fatigue	0 - 4 listed above
Weakness	0 - No weakness - Strong in all muscle groups & have no problems with their muscle strength or ability to do things compared to their peers
	1 - Mild Weakness - Almost normal strength in all muscles & can do almost everything with their muscles that their peers can do with minimal/mild problems
	2 - Moderate Weakness - Their muscles are somewhat weak; can do things with their muscles, but using their muscles for many things is hard for them)
	3 - Severe Weakness - Their muscles are very weak & using their muscles for most things is hard for them; they need assistance with some things)
	4 - Extremely Severe Weakness - Their muscles are extremely weak & using their

MH Study Team

Name: _____

Reviewer Signature: _____

Date Reviewed: _____

SAVI Diary

Date of last clinic visit: _____ **Study #:** _____ **Subject #** _____ **Month/Year of this diary page:** _____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

Total Daily Dose _____ **(mg)**

Dose breakdown _____ **(mg)**

Dose Frequency - circle or check one. (number of doses per day)

If your dose or dose frequency changes, start a new diary page starting with the current calendar day.

- 1 time per day ☐
- 2 times per day ☐
- 3 times per day ☐
- 4 times per day ☐
- 5 times per day ☐

	Fever	Rash	Musculo-skeletal Pain	Fatigue	Respiratory/ Breathing Symptoms	Ulcers / Ischemic lesions
0	0 - No fever	0 - No rash	0 - No pain	0 - No fatigue	0 - No breathing problems	0 - No ulcers
1	1 - Fever without impact on daily activity	1 - Rash barely present	1 - Mild pain not requiring medication, no limping	1 - Mild fatigue, no functional impact	1 - Mild breathing problems / rapid breathing / coughing, no functional impact	1 - Few ulcers, only in 1 location and/or no drainage, no ischemia
2	2 - Fever requiring fever-reducing medication or with mild impact on daily actitivity	2 - Rash covering 10% of body surface area	2 - Pain requiring medication or leading to limping or other mild functional impact	2 - Moderate fatigue with mild functional impact	2 - Moderate breathing problems / rapid breathing / coughing with mild functional impact	2 - Ulcers in more than 1 location and/or with some drainage, no ischemia
3	3 - Fever requiring medication with significant impact on daily activities (missing school, listlessness)	3 - Rash covering more than 30% of body surface area	3 - Pain requiring medication or having a severe functional impact	3 - Severe fatigue with a severe functional impact	3 - Severe breathing problems / rapid breathing / coughing with a severe functional impact	3 - Ulcers in multiple locations and/or significant drainage, and/or any ischemia
4	4 - Fever forcing the patient to be bedridden	4 - Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 - Severe pain, child refusing to walk, or staying in bed most of the time	4 - Severe fatigue resulting in patient staying in bed most of the time	4 - Severe breathing problems / rapid breathing / coughing which result in patient staying in bed most of the time	4 - Severe ulcers / ischemic lesions in multiple locations

Day	Date MM/DD/YYYY	Total Daily JAGA Dose Given (mg)	Missed JAGA Dose & Reason	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Fatigue	Respiratory/ Breathing Symptoms	Ulcers / Ischemic lesions	Dose of Steriods (mg)	Peak Flows	Name or initials of person entering information, each day
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
13													
14													
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31													

NIH Study Team

Name: _____ Reviewer Signature: _____ Date Reviewed: _____

AGS Patient Daily Diary

					0 = Abl e to perform all activities of daily living independently with no		**0** = sleeps more than 3 hours for infants less than 6 months; more than 6 hours for children over 6 months				0 = No			
					5 = Able to participate in the following with some level of disability: ambulation, communication or fine motor	**1** = inconsolable >2 minutes **OR** cry intermittently for <10 minutes"	**1** = sleeps 2-3 hours at a time for infants less than 6 months; more than 4-5 hours for children over 6 months				**1** = Consoling calms infant in 2-5 minutes	**1** = Blotchy red rash which comes and goes	**1** = Blotchy red rash which comes and goes
Dose Frequency - circle or check one. (number of doses per day) If your dose or dose frequency changes, start a new diary page starting with the current day.		**1 time per day 2 times per day 3 times per day 4 times per day**			**7** = Requires functional or equipment support for any of the following: ambulation, communication or fine mortor	2 = inconsolable >2 minutes **AND** cry intermittently for >10 minutes	**2** = sleeps 1-2 hours for infants less than 6 months; more than 2-3 hours for children over 6 months				**2** = Consoling calms infant in 6-15 minutes	**2** = Persistently red spots which stay	**2** = Persistently red spots which stay
					10 = Dependent for all activities of daily living and unable to ambulate, communicate or perform fine motor tasks even with support	**3** = Inconsolable for > 10 minutes	**3** = sleeps <1 hour for infants less than 6 months; greater than 1-2 hours for children over 6 months	**8** = Tonic-clonic, subtle staring, chewing,	**1** = Temperature greater than or equal to 37.3°C		**3** = Consoling calms in more than 15 min or	**3** = Persistent spots which do not blanche when pressed	**3** = Persistent spots which do not blanche

	Date MM/DD/YYY	Total Daily Dose JAGA (mg) Given	Missed JAGA Dose (mg) &				Length of Uninterrupted	Generalized Seizure		Excessive Irritabilit	Skin Findings	Skin Findings, hands, feet,	Name or initials of person entering information, each
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
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31													

Site Study Team

Reviewer Name: Reviewer Signature: Date Reviewed:

Appendix 4. National Institutes of Health (NIH) Natural History Protocol

All patients treated at the NIH are enrolled in an observational study entitled "Studies of the Natural History, Pathogenesis, and Outcome of Autoinflammatory Diseases (NOMID/CAPS, DIRA, CANDLE, SAVI, CRMO, Still's Disease, Behcet's Disease, and Other Undifferentiated Autoinflammatory Diseases)," hereafter referred to as the Natural History Protocol (NCT00059748). The NIH operates this Natural History Protocol in order to study the signs and symptoms and to gather more information about the cause and courses of these autoinflammatory diseases. All patients being treated in JAGA at NIH are also enrolled in the Natural History Protocol. Some additional efficacy data associated with baricitinib treatment are available through the Natural History Protocol including laboratory data (eg. C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], interferon signature), additional assessments (Physician's Global Assessment of Disease Activity [PGA], Pain Global Assessment, Childhood Health Assessment Questionnaire [CHAQ], Pediatric Quality of Life Inventory [PedsQL]), and photographic documentation of treatment responses. The Natural History Protocol provides the appropriate patient consent to allow sharing of data collected in the protocol with Lilly and will be used to supplement JAGA data and provide further evidence of efficacy.

Laboratory results, photographs, and results at each visit from the PGA, Pain Global Assessment, CHAQ, and PedsQL will be transferred from NIH to Lilly. By-patient listings of laboratory results and additional assessments (summary score and change from baseline for the PGA, Pain Global Assessment, CHAQ, and PedsQL) will be provided.

The following laboratory results and assessments may be transferred from NIH to Lilly:

- ESR (first result)
- ESR (second result, if any)
- CRP (first result)
- CRP (second result, if any)
- Lactate dehydrogenase (LDH)
- Ferritin
- Iron
- Transferrin
- % Saturation
- Aldolase
- Anti-Nuclear Antibody (ANA)
- Serum Osteocalcin

- Thyroid Stimulating Hormone (TSH)
- Thyroxine, Free (T4)
- Erythropoietin
- Cystatin C
- Protein Creatinine Ratio, Urine
- Urine WBC
- Urine RBC
- CD3#
- CD3%
- CD4/CD3#
- CD4/CD3%
- CD8/CD3#
- CD8/CD3%
- Natural killer (NK) cells#
- NK%
- CD19#
- CD19%
- Immunoglobulin (Ig)G
- IgA
- IgM
- IgE
- Abdominal Girth
- Interferon Signature

Physician Global Assessment of Disease Activity [PGA]:

The investigator will be asked to give an overall assessment of the severity of the subject's current RA activity using a 100-mm horizontal visual analog scale (VAS), where the left end (0) represents no disease activity and the right end (100) represents extremely active disease.

Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick.

Pain Global Assessment:

Subjects will be asked to give an overall assessment of their pain severity using a 100-mm horizontal VAS where the left end (0) represents no pain and the right end (100) represents extreme pain.

Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick.

Childhood Health Assessment Questionnaire [CHAQ]:

The Childhood Health Assessment Questionnaire (CHAQ) assesses functional health status in children aged 6 months to 18 years. The 30- item CHAQ captures 8 functional areas (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities). The CHAQ is either parent or self-administered with recall "Over the Past week". Items are scored on a 4-point scale ranging from 0 "Without Any Difficulty", 1 "With Some Difficulty", 2 "With Much Difficulty", 3 "Unable To Do" or "Not Applicable" with lower scores indicating better functioning. The highest score for any component question determines the score for that category. If a component question is left blank or the response is too ambiguous to assign a score, then the score for that category is determined by the remaining completed question(s). If all component questions are blank, then the category is left blank. The CHAQ disability index (DI) is calculated by adding the scores for each of the categories and dividing by the number of categories answered. This gives a score in the 0-3.0 range. Only the total score for the CHAQ (CHAQ DI) will be transferred from NIH to Lilly, and so it is assumed that the score was calculated correctly by NIH.

Pediatric Quality of Life Inventory [PedsQL]:

The Pediatric Quality of Life Inventory (PedsQL) is a modular instrument designed to measure health-related quality of life (HRQoL) in children and adolescents aged 2-18 years. The 23-item PedsQL Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL disease-specific modules. The PedsQL captures HRQoL domains including physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). Items are scored using a 5-point Likert scale from 0 (Never) to 4 (Almost always) where higher scores indicate better HRQoL. If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. Only the total score for the PedsQL will be transferred from NIH to Lilly, and so it is assumed that the score was calculated correctly by NIH. The PedsQL total score is the sum of all of the items divided by the number of items answered on all the scales.

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Approver: PPD
Approval Date & Time: 02-May-2019 19:24:05 GMT
Signature meaning: Approved

1. Statistical Analysis Plan: Compassionate Use Treatment I4V-MC-JAGA: Treatment of Conditions Expected to Benefit from JAK 1/2 Inhibition: CANDLE, CANDLE-Related Conditions, SAVI, and Severe Juvenile Dermatomyositis

Baricitinib (LY3009104)

Study I4V-MC-JAGA is an open-label compassionate use treatment program to provide baricitinib to patients with conditions expected to benefit from JAK inhibition: CANDLE, CANDLE-related conditions, SAVI, and severe juvenile dermatomyositis. Patients will receive an intial dose based on their weight class and disease type that may be escalated to determine a tolerable dose. Patients may be dosed for up to 288 weeks. It is anticipated that up to 35 patients may be treated with baricitinib in an individualized manner. The treatment guidelines contained herein are for compassionate use only. With in these guidelines, open-label baricitinib will only be administered to patients who meet inclusion and exclusion criteria.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I4V-MC-JAGA

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on date provided below.

Approval Date: 29-Apr-2016 GMT

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3. Revision History

The I4V-MC-JAGA (JAGA) program is an open-label expanded access/compassionate use treatment program. While an SAP is out of scope for such programs as JAGA, the development of an SAP was undertaken in order to document planned handling of data from Study JAGA to support a regulatory submission. Study JAGA SAP Version 1 was approved prior to the interim database lock intended to support a regulatory submission (type B briefing document).

4. Study Objectives

4.1. Primary Objective

The primary objective is to determine if the administration of baricitinib to patients with Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE), CANDLE-related conditions, Stimulator of Interferon Genes (STING)-Associated Vasculopathy with Onset during Infancy (SAVI), or Juvenile Dermatomyositis (JDM) results in reduction in the patient's mean daily diary scores as follows:

- CANDLE diary: reduction in mean daily score to <0.5
- SAVI diary: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and respiratory/breathing symptoms score <1.0 increase from baseline
- JDM diary: reduction in mean score by 1 point in at least 3 categories.

4.2. Secondary Objectives

The secondary objectives of the study are:

- to determine, in patients receiving steroids at baseline, if administration of baricitinib to patients with CANDLE, CANDLE-related conditions, or SAVI results 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, in patients receiving steroids at baseline, if the administration of baricitinib to patients with severe JDM results in a decrease in the daily dose of corticosteroids (systemic corticosteroids <0.2 mg/kg/day oral prednisone or a decrease of at least 25% of the patient's daily dose at baseline).
- to determine if the administration of baricitinib to patients with severe JDM results in a reduction in the patient's mean diary score to <1.0.

5. Study Design

5.1. Summary of Study Design

Study JAGA is an open-label compassionate use treatment program for patients who weigh at least 8.5 kg and are at least 17.5 months of age (patients who weigh less than 8.5 kg or are younger than 17.5 months may be considered for enrollment after discussion with the Sponsor). Patients will receive an initial dose based on their disease type and weight class. The dose may be escalated to determine a tolerable level. The patient's disease severity will be recorded by the patient or caregiver in a patient daily diary 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 steroids), as appropriate.

Figure JAGA.5.1. illustrates the study design.

5.2. Determination of Sample Size

Because this study of baricitinib is designed for compassionate use and the conditions being treated are rare, there is no minimum or maximum requirement of the number of patients to be studied.

5.3. Method of Assignment to Treatment

The study is an open-label trial with no randomization. All patients participating in this study will receive baricitinib.

5.3.1. Treatment Administered

All eligible patients will receive treatment with baricitinib as a twice-daily dose, once-daily dose, or multiple divided doses (as described in Protocol Section 7.1). Patients will receive an initial dose based on their weight class and disease type; patients in the upper weight classes may have their dose escalated to determine a tolerable dose. Dose escalation will be performed up to the maximum allowable dose level, as long as there are no safety concerns that would preclude increasing the dose.

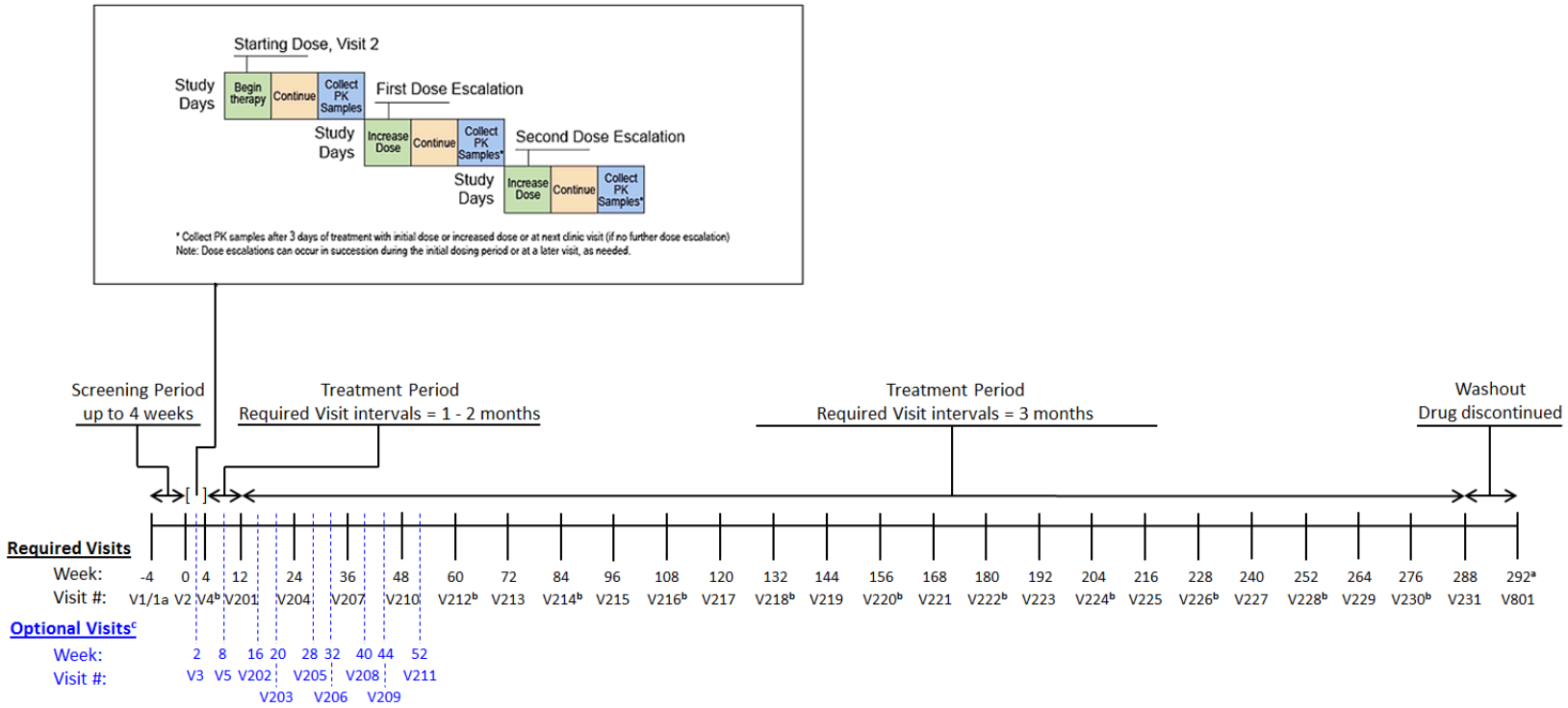

Figure JAGA.5.1. Clinical Protocol I4V-MC-JAGA(r) study design.

Abbreviations: PK = pharmacokinetics; V = visit.

[a] V801 should occur approximately 28 days after the last dose of investigational product.

[b] These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally.

[c] Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained locally.

6. A Priori Statistical Methods

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

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly).

6.1. General Considerations

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Because the medical conditions being treated in this study are rare, it is anticipated that relatively few patients will be enrolled. Due to variable visit windows between patients, summaries by visit will not be provided. Therefore, data listings will be the primary tool used to summarize the results from this study with additional summary statistics (as appropriate).

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

When summary statistics are deemed appropriate, continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. When summary statistics are deemed appropriate, categorical data will be summarized as frequency counts and percentages.

The endpoint will be considered the last non-missing assessment while on study drug.

Week will be calculated as the number of weeks after the first dose of baricitinib.

All analyses will be implemented using SAS Version 8.2 or a more recent version.

6.1.1. Definition of Baseline and postbaseline Measures

The treatment period starts after administration of the first dose of baricitinib at Visit 2 (Week 0) and ends on the date of the final visit in the treatment period or the early discontinuation visit. The endpoint will be the last non-missing postbaseline measurement during the treatment period.

Baseline of the treatment period will be defined as the last available value on or before the first dose of baricitinib. In most cases, this will be the measure recorded at Week 0 (Visit 2).

Change from baseline will be calculated as the visit value of interest minus the baseline value.

Any measurement collected after the first dose of baricitinib will be considered a postbaseline measurement.

Baseline of the washout period is defined as the date of the final visit or early termination in the treatment period. Endpoint of the washout period is Visit 801.

6.2. Handling of Dropouts or Missing Data

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

6.3. Use of an "Efficacy Subset" of Patients

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

Enrolled population set includes all patients who have entered the study and who are not considered screen fails at Visit 2 (i.e. patients not excluded due to not meeting inclusion criteria or meeting exclusion criteria at Visit 2).

Safety population set includes all enrolled patients who receive at least 1 dose of baricitinib and who did not discontinue the study for the reason "Lost to Follow-up" at the first postbaseline visit (Visit 3).

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

6.4. Patient Disposition

The following patient disposition summaries will be provided:

- Frequency counts and percentages of patients who were screen fails (excluded at Visit 2 prior to receiving baricitinib) will be provided.
- Frequency counts and percentages of patients who complete or discontinue early from the study will be summarized separately by disease diagnosis along with their reason for study discontinuation.
    - Among patients who completed the study, frequency counts and percentages of patients who completed the safety closeout visit, or did not complete the safety closeout visit will be presented by disease diagnosis.
    - Among patients who discontinued early from the study, frequency counts and percentages of patients who completed the safety closeout visit or did not complete the safety closeout visit will be presented by disease diagnosis.

A listing of patient disposition during the treatment period will be provided for all enrolled patients who have completed or discontinued from the treatment period, with the date of enrollment, the duration of their participation in the study (days and years), last completed visit, date of last completed visit, the primary reason for study discontinuation, and additional details that support the reason for discontinuation. If the reason for discontinuation is an adverse event (AE), then the preferred term will be specified. If the reason for discontinuation is death, the date of death and related AE or other reason for death will be specified. A separate disposition listing will be provided for patients who entered the washout period.

A by-patient listing of reason for screen failure including the visit that occurred will be provided. The number of patients who entered the study, enrolled in the study, and are included in the safety population will be summarized.

6.5. Patient Characteristics

Patient characteristics including demographics will be summarized by disease diagnosis. The following continuous demographic and baseline characteristic variables will be summarized using descriptive statistics.

- Age at the time of study entry (in years).
- Height (cm)
- Weight (kg) (as recorded at Visit 2, unless missing, in which case the Visit 1 result will be used).

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

- Sex
- Weight categories (kg) (<20, ≥20 - <30, ≥30 - <40, ≥40 - <50, ≥50 - <60, and ≥60)
- Race
- Ethnicity

Baseline is defined as in Section 6.1.1 unless otherwise specified.

A by-patient listing of demographic and baseline characteristics will be provided including age at study entry (years and months), body weight (kg), height (cm), body mass index (BMI), and BMI percentile. A by-patient listing of demographic and other characteristics at endpoint will be provided with duration on study (years), age, weight, height, BMI, and BMI percentile.

6.6. Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary. Medication start and stop dates will be compared to the date of the first dose of study treatment (recorded on the Study Drug Administration page of the electronic case [clinical] report form [eCRF]) to allow medications to be classified as 'prior' or 'concomitant'.

Medications that start and end before the first dose date will be classified as 'prior' medications. Medications that end on or after the first dose date will be classified as 'concomitant' medications. Note that medications with partial or missing start and/or stop dates will be assumed to be 'concomitant' unless there is evidence, through comparison of partial dates, to suggest otherwise.

A by-patient listing of all non-steroid concomitant medications will be provided including therapy type (prior or concomitant), preferred term, reported term, start and end date, start and end week, a flag if the medication was started after the last dose of baricitinib, and indication. A separate by-patient listing of steroid concomitant medications will be provided including therapy type (prior or concomitant), preferred term, reported term, start and end date, start and end week, frequency, route, and a flag if the medication was started after the last dose of baricitinib.

Non-steroid and steroid concomitant medications will be summarized separately by preferred term.

6.7. Efficacy Analyses

Efficacy analyses will use the efficacy population defined in Section 6.6.

6.7.1. Primary Analyses

The primary objective is to determine if the administration of baricitinib to patients CANDLE, CANDLE-related conditions, SAVI, or JDM results in reduction in the patient's mean daily diary scores as follows:

- CANDLE diary: reduction in mean daily score to <0.5
- SAVI diary: reduction in mean daily score, exclusive of respiratory/breathing symptoms, to <1.0 and respiratory/breathing symptoms score <1.0 increase from baseline
- JDM diary: reduction in mean score by 1 point in at least 3 categories.

A by-visit listing of the calculated mean diary score (defined in Section 6.8.1), change in diary score, percent change in diary score, mean symptom scores, and change from baseline in each symptom score will be provided. The number and percentage of patients achieving a decrease in the appropriate diary score will be summarized using the listing.

6.7.2. Secondary Efficacy Analyses

The secondary objectives of the study are:

- to determine, in patients receiving steroids at baseline, if administration of baricitinib to patients with CANDLE, CANDLE-related conditions, or SAVI results 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, in patients receiving steroids at baseline, if the administration of baricitinib to patients with severe JDM results in a decrease in the daily dose of corticosteroids (systemic corticosteroids <0.2 mg/kg/day oral prednisone or a decrease of at least 25% of the patient's daily dose at baseline).

to determine if the administration of baricitinib to patients with severe JDM results in a reduction in the patient's mean diary score to <1.0.

The total daily corticosteroid dose (mg), corticosteroid dose per weight (mg/kg), change from baseline, and percent change from baseline of corticosteroid doses will be listed. The number and percentage of patients achieving a reduction in corticosteroid dose will be summarized using the listing.

6.7.3. Additional Analyses of the Primary Outcome

Additional summaries (where applicable) and listings by patient sub-populations (eg. age, sex) may be created as appropriate.

6.7.4. Other Secondary Efficacy Analyses

A by-patient listing of maximum baricitinib dose (mg), maximum dose per weight (mg/kg), maximum reduction in steroid dose (mg), percent maximum reduction in steroid dose (%), maximum reduction in steroid dose per weight (mg/kg), percent maximum reduction in steroid dose per weight (%), minimum mean diary score, and minimum diary score by symptom will be provided. Figures will be generated as appropriate.

6.8. Health Outcomes/Quality-of-Life Analyses

See Appendix 4. A separate SAP will be developed for psychometric validation work, as necessary, for the patient diaries by Global Patient Outcomes and Real World Evidence (GPORWE).

6.8.1. Patient Diary and Diary Score

The CANDLE and CANDLE-Related Diary is a daily assessment of disease severity completed by the patient (if able), parent/caregiver, or healthcare provider/medical staff. The diary assesses 5 prominent disease symptoms (fever, rash, musculoskeletal pain, headache, and fatigue) with each symptom scored on a 5-point numeric rating scale ranging from 0 (no symptom) to 4 (severe symptom) as shown below in Table JAGA.6.1. The respondent writes in the value that best corresponds to the severity of the symptom on that day.

Table JAGA.6.1. CANDLE and CANDLE-Related Diary Scores

0 = No fever	0 = No rash	0 = No pain	0 = No headache	0 = No fatigue
1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild headache not requiring medication or any adjustments of daily activities	1 = Mild fatigue, no functional impact
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	2 = Rash covering 10% of body surface area	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Headache requiring medication or having mild functional impact	2 = Moderate fatigue with mild functional impact
3 = Fever requiring medication with significant impact on daily activities (missing school, listlesness)	3 = Rash covering more than 30% of body surface area	3 = Pain requiring medication or having a severe functional impact	3 = Headache requiring medication and having a severe functional impact	3 = Severe fatigue with a severe functional impact
4 = Fever forcing the patient to be bedridden	4 = Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	4 = Severe fatigue resulting in patient staying in bed most of the time

Abbreviation: CANDLE = Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature.

The SAVI Diary is a daily assessment of disease severity completed by the patient (if able), parent/caregiver, or healthcare provider/medical staff. The diary assesses 6 prominent disease symptoms (fever, rash, musculoskeletal pain, fatigue, respiratory/breathing symptoms, and ulcers/ischemic lesions) with each symptom scored on a 5-point numeric rating scale ranging from 0 (no symptom) to 4 (severe symptom) as shown below in Table JAGA.6.2. The respondent writes in the value that best corresponds to the severity of the symptom on that day.

Table JAGA.6.2. SAVI Diary Scores

0 = No fever	0 = No rash	0 = No pain	0 = No fatigue	0 = No breathing problems	0 = No ulcers
1 = Fever without impact on daily activity	1 = Rash barely present	1 = Mild pain not requiring medication, no limping	1 = Mild fatigue, no functional impact	1 = Mild breathing problems / rapid breathing / coughing, no functional impact	1 = Few ulcers, only in 1 location and/or no drainage, no ischemia
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	2 = Rash covering 10% of body surface area	2 = Pain requiring medication or leading to limping or other mild functional impact	2 = Moderate fatigue with mild functional impact	2 = Moderate breathing problems / rapid breathing / coughing with mild functional impact	2 = Ulcers in more than 1 location and/or with some drainage, no ischemia
3 = Fever requiring medication with significant impact on daily activities (missing school, listlesness)	3 = Rash covering more than 30% of body surface area	3 = Pain requiring medication or having a severe functional impact	3 = Severe fatigue with a severe functional impact	3 = Severe breathing problems / rapid breathing / coughing with a severe functional impact	3 = Ulcers in multiple locations and/or significant drainage, and/or any ischemia
4 = Fever forcing the patient to be bedridden	4 = Worst rash ever or covering over 30% of body surface area or hurting or stinging	4 = Severe pain, child refusing to walk, or staying in bed most of the time	4 = Severe fatigue resulting in patient staying in bed most of the time	4 = Severe breathing problems / rapid breathing / coughing which result in patient staying in bed most of the time	4 = Severe ulcers / ischemic lesions in multiple locations

Abbreviation: SAVI = Stimulator of Interferon Genes (STING)-Associated Vasculopathy with Onset during Infancy.

The JDM Diary is a daily assessment of disease severity completed by the patient (if able), parent/caregiver, or healthcare provider/medical staff. The diary assesses 6 prominent disease symptoms (fever, rash, musculoskeletal pain, headache, fatigue, and weakness) with each symptom scored on a 5-point numeric rating scale ranging from 0 (no symptom) to 4 (severe symptom) as shown below in Table JAGA.6.3. The respondent writes in the value that best corresponds to the severity of the symptom on that day.

Table JAGA.6.3. JDM Diary Scores

0 = No fever	**0** = No rash	**0** = No pain	**0** = No headache	**0** = No fatigue	0 = No muscle
1 = Fever without impact on daily activity	**1** = Rash barely present	**1** = Mild pain not requiring medication, no limping	**1** = Mild headache not requiring medication or any adjustments of daily activities	**1** = Mild fatigue, no functional impact	1 = Mild weakness
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	**2** = Rash generally brighter pink to red	**2** = Pain requiring medication or leading to limping or other mild functional impact	**2** = Headache requiring medication or having mild functional impact	**2** = Moderate fatigue with mild functional impact	2 = Moderate weakness
3 = Fever requiring medication with significant impact on daily activities (missing school, listlesness)	**3** = Rash generally bright red	**3** = Pain requiring medication or having a severe functional impact	**3** = Headache requiring medication and having a severe functional impact	**3** = Severe fatigue with a severe functional impact	3 = Severe weakness
4 = Fever forcing the patient to be bedridden	**4** = Worst rash ever	**4** = Severe pain, child refusing to walk, or staying in bed most of the time	**4** = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	**4** = Severe fatigue resulting in patient staying in bed most of the time	4 = Extremely severe weakness

Abbreviation: JDM = juvenile dermatomyositis.

At each visit, the investigator calculates the average score for each symptom being collected on the diary (that is, the average of the daily scores since the previous visit, correcting for any day for which diary scores were not recorded). The average diary score assessed over at least 2 weeks prior to entry, if available, will be used for Visit 1. Otherwise, patients can complete the diary after study consent is signed for at least a 2-week timeframe during the screening period and meet the inclusion criteria for enrollment into the study at Visit 2. The investigator 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. Only the average symptom scores at each visit (calculated by the investigator/site personnel) and the mean diary score at each visit (calculated by the investigator/site personnel) are entered into the JAGA database. The average diary score at each visit will be re-calculated based on the average symptom scores at each visit that were entered in the JAGA database. Additionally, the average diary score for SAVI patients will be calculated as the average of the symptom scores excluding the respiratory/breathing symptom score. If more than 50% symptom scores are missing for the specified calculation then the average diary score will not be calculated.

No formal psychometric validation (per the Food and Drug Administration [FDA] patient-reported outcome [PRO] guidance) has been completed for the diary given the rarity of CANDLE Syndrome and resulting small number of patients assessed using the diary. However, similar types of diaries have been used to study conditions such as neonatal-onset multisystem inflammatory disease (NOMID) and have supported associated label updates (anakinra [Kineret®]; [Goldbach-Mansky et al. 2006]). The cut-off for determining response (<0.5 and <1.0 for CANDLE/CANDLE-Related and SAVI patients, respectively) were based on investigator judgment based on previous experience with NOMID patients. The same cut-offs were used in NOMID patients.

6.9. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Venous blood samples for the measurement of baricitinib concentrations will be collected from patients enrolled in the study. Samples were collected at the following time points:

- **First Dose Escalation (Inpatient Dose Escalation,** Table JAGA.7.1 from protocol**).** Four samples will be collected: predose and at approximately 1, 1.5, and 4 hours postdose at the following times: (1) on the third day after the start of baricitinib therapy and (2) on the third day after the dose increase. Alternatively, patients can be discharged from the hospital on the day of the dose increase and the second pharmacokinetic (PK) sampling can occur at the next clinic visit.
- **Second Dose Escalation** (Table JAGA.7.2 from protocol)**.** Six samples will be collected: predose (morning dose) and approximately 1, 1.5, and 4 hours postdose (morning dose); predose (evening dose) and approximately 1.5 hours postdose (evening dose) at the following times: (1) on the third day after the first dose increase and (2) on the third day after the second dose increase. Alternatively, the second PK sampling can occur at the next clinic visit.

Pharmacokinetic data for baricitinib will be analyzed using a population modeling approach via a nonlinear mixed-effects modeling (NONMEM) program. One- and 2-compartment structural models with first- or zero-order absorption will be tested. A first-order absorption 1-compartment model will be parameterized in terms of absorption rate constant (Ka), central compartment clearance (CL), and central compartment volume of distribution (V1). The 2-compartment model will be parameterized in terms of Ka, V1, CL, intercompartmental clearance, and peripheral volume of distribution (V2). In the case of a zero absorption model, the absorption model will be parameterized by "absorption duration" (D1). Previous modeling results in healthy subjects and patients with Rheumatoid Arthritis (RA) and known predominant renal elimination characteristics of baricitinib indicated close correlation of baricitinib exposures with renal function defined by Modification of Diet in Renal Disease- estimated Glomerular Filtration Rate (MDRD-eGFR); hence, partitioning of total clearance into renal and nonrenal clearance might also be incorporated into the model. Interpatient variability will be assessed separately on each of the PK parameters using an exponential error structure. Residual error will be assessed as proportional, additive, and combined proportional and additive error structures. Intrinsic factors such as age; body weight; sex; renal function; transaminases/albumin/bilirubin,

which are representative of hepatic function will be investigated to assess their influence on PK parameters such as clearance and volume of distribution, where applicable, if data permits.

Because this study of baricitinib is designed for compassionate use and the sample size is small, no formal PK/pharmacodynamic (PD) analysis is planned for this study. Exploratory analyses may be conducted to evaluate the relationship between baricitinib exposure and the clinical endpoint of daily diary scores if data permit. Other analyses for assessing PKPD relationship may be conducted, if deemed appropriate.

6.10. Safety Analyses

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

6.10.1. Extent of Exposure

A by-patient listing will be created including the visit, week, patient's weight, total daily dose, dose frequency, the treatment start date or dose adjustment date, dose adjustment type (increase, decrease, omitted, and treatment schedule changed), and reason dose adjusted.

Baricitinib exposure will be summarized including frequency counts and percentages of patients who have taken baricitinib in subset of months (>0-6, >6-12, >12-18, >18-24, >24-30, >30-36, >36-42, >42-48, >48-54, >54-60, and >60 months), duration of exposure to baricitinib (months and years), and the patient years of exposure (PYE) will be summarized. Patient years of exposure is defined as the sum of all patient exposure time in years for the specific disease diagnosis. A by-patient listing of study drug exposure will be provided including duration of exposure in years and weeks. Duration in days of baricitinib exposure is defined as the date of last dose of baricitinib minus the date of first dose of baricitinib +1.

6.10.2. Adverse Events

Adverse events are classified based upon the Medical Dictionary for Regulatory Activities (MedDRA). Each AE will be coded to system organ class (SOC) and Preferred Term (PT) using the MedDRA version that is current at the time of database lock. Severity of AEs is recorded as mild, moderate, or severe. Adverse events will use the safety population defined in Section 6.6.

Summaries will consist of the frequency and percent of patients experiencing each AE. For summaries, SOC will be sorted in alphabetical order and PT in decreasing frequency within SOC by the total group. Patients will only be counted once, regardless of how many conditions are included under the same SOC and PT. For events that are sex-specific, the denominator and computation of the percentage will include only patients from the given sex.

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

6.10.2.1. Adverse Events

An overview of AEs including deaths, SAEs, TEAEs, and patients discontinued from study due to an AE will be summarized for the treatment period. An overview of AEs including deaths, SAEs, discontinuation-emergent adverse events (DEAE), and patients discontinued from study due to an AE will be summarized for the washout period.

Pre-existing conditions are defined as any physical complaints/symptoms (AEs) that present prior to initiation of treatment with baricitinib and do not worsen in severity after starting baricitinib treatment. The frequency and percentage of patients who experienced pre-existing condition will be summarized by disease diagnosis using PT nested within SOC.

6.10.2.2. Serious Adverse Events

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

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

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The number and percentage of patients who experienced any SAE will be summarized by disease diagnosis using PT nested within SOC for the treatment period and for the washout period, separately.

6.10.2.3. Treatment-emergent Adverse Events

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

Treatment-emergent (AEs) will be summarized by MedDRA PT nested within cluster with clusters ordered alphabetically, and events ordered within each cluster by decreasing frequency, including the PYE and the exposure adjusted incidence rate (EAIR). Clusters will be groups of preferred terms that the medical team determines are linked or similar. Exposure adjusted incidence rate is expressed as the number of patients experiencing an adverse event per 100 patient years of exposure to treatment and is derived as 100 times the incidence of the event divided by the sum of all patient exposure time (in years for the specific disease diagnosis).

6.10.2.4. Discontinuation-Emergent Adverse Events

Adverse events will be considered DEAEs if the AEs begin or increase in severity after the last visit during the treatment period. If the maximum severity during the washout period is greater than the treatment period severity, the event is considered to be discontinuation-emergent. Discontinuation-emergent AEs will be summarized by SOC and PT.

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

6.10.3.1. Adverse Events of Special Interest

Adverse events of special interest include the following:

- Infections
- myelosuppressive events
    - anemia (hemoglobin <6.5 g/dL),
    - leukopenia (White blood cell [WBC] count <2000 cells/μL),
    - neutropenia (absolute neutrophil count [ANC] <1000 cells/μL),
    - lymphopenia (lymphocyte count <500 cells/μL), and
    - thrombocytopenia (platelet count <75,000/μL)
- thrombocytosis (platelet count >600,000/μL)
- elevations in alanine transaminase (ALT) or aspartate aminotransferase (AST) (>3 times upper limit of normal [ULN]) with total bilirubin (>2 times ULN).

Treatment-emergent infection AESIs will be summarized by disease diagnosis using PT nested within the SOC of infections and infestations. Infection AESIs will be provided in a listing.

Adverse events of special interest based on laboratory data and according to the definitions listed above will be summarized. A by-patient listing of laboratory results at all visits for the laboratory analyte associated with a specific AESI (anemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia, thrombocytosis, or abnormal ALT or AST with elevated bilirubin) will be created.

6.10.4. Clinical Laboratory Evaluation

Hematology, chemistry, urinalysis, and fasting lipids laboratory measurements will be analyzed by local laboratories, and will be collected in the conventional (CN) units that the local laboratory uses to measure each analyte. The CN units will require conversion to standardized Système International (SI) units for listing purposes. Observed values (CN and SI) for hematology, chemistry, urinalysis, and fasting lipids laboratory parameters will be listed separately for each patient, including visit, week of visit, values, units, reference ranges, and flag for low/high results.

The frequency count and percentage of patients with treatment-emergent abnormalities (high, low, abnormal) in laboratory results at any time postbaseline will be summarized for patients at risk (those with normal baseline values with respect to the direction of the abnormality of interest and have at least one postbaseline measure). A similar summary will be created for treatment-emergent abnormalities in laboratory results at endpoint.

Abnormal elevations in ALT will be summarized as follows:

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

6.10.5. Vital Signs and Other Physical Findings

Graphical displays of individual patient data for pulse, systolic blood pressure, diastolic blood pressure, and weight over time with associated tables of values and changes from baseline will be created.

6.11. Protocol Violations

Protocol deviations will be tracked by the clinical team, and the following categories of important protocol deviations will be reported:

- inclusion/exclusion deviations,
- improper administration of the informed consent,
- prohibited medication,
- protocol non-compliance,
- missing procedures,
- and study drug administration and compliance deviations

A summary of the number and percentage of patients with an important protocol deviation by disease diagnosis and by type of deviation will be provided. A listing of important protocol deviations will be provided with any additional details.

6.12. Interim Analyses and Data Monitoring

An interim analysis is planned after all patients with CANDLE Syndrome who have completed at least 1 year of treatment with baricitinib or have discontinued from Study JAGA. The purpose of the interim analysis is to support regulatory submission of the Study JAGA data. Adjustment to type I error is not applicable as Study JAGA is a single arm, open-label program.

6.13. Annual Report Analyses

No other analyses planned for annual report.

6.14. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements. Analyses provided for the CTR requirements include the following: A summary of AEs will be provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients in the treatment group may not be included if a 5% threshold is chosen.

7. References

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.

8. Appendices

Appendix 1. Protocol I4V-MC-JAGA Study Schedule

Study Schedule, Protocol I4V-MC-JAGA(r)

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Informed consent		X										
Demographic characteristics		X										
Height		X		X	X	X	X	X	X	X	X	X
Weight		X		X	X	X	X	X	X	X	X	X
Administer tuberculosis test		X[f]										
Read tuberculosis test			X									
Chest x-ray		X[g]										
Electrocardiogram (ECG)		X										
Review inclusion/exclusion criteria		X										
Medical history		X										
Physical examination		X										
Assessment of JDM core measures[h]		X										
Vital signs		X		X	X	X	X	X	X	X	X	X
Diary Scores		X		X[i]	X	X	X	X	X	X	X	X
Concomitant medications		X		X	X	X	X	X	X	X	X	X
Preexisting conditions		X										

Study Schedule, Protocol I4V-MC-JAGA(r)

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Adverse events				X	X	X	X	X	X	X	X	X
Investigational drug dose modifications				X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]		
Investigational product returned and compliance assessed					X	X	X	X	X	X		
Laboratory												
Hematology		X		X[l]	X	X	X	X	X	X	X	X
Serum chemistry		X		X[l]	X	X	X	X	X	X	X	X
Fasting lipid panel		X					X	X	X	X	X	
Urinalysis		X		X[l]	X	X	X	X	X	X	X	X
HBsAg, HBcAb, HBsAb		X[m]										
Hepatitis C antibody		X[m]										
HIV		X[m]										
Thyroid stimulating hormone		X[f]										
Serum pregnancy test[n]		X										

Study Schedule, Protocol I4V-MC-JAGA(r)

		Screening		Initial Dosing Period	Treatment						Early Termination	Safety Closeout
Visit number	**Required**	**1**	**1a**	**2**		**4[q]**		**201**	**204, 207, 210**	**212[q], 213, 214[q], 215, 216[q], 217, 218[q], 219, 220[q], 221, 222[q], 223, 224[q], 225, 226[q], 227, 228[q], 229, 230[q], 231**	**ET[a]**	**801**
	Optional[r]				**3**		**5**		**202, 203, 205, 206, 208, 209, 211**			
Weeks from enrollment		**4 to .5**		**0**	**2**	**4**	**8**	**12**	**16 to 52[b]**	**60 to 288[c]**	**–**	**292**
Number of days at visit		**28 to 2**		**Variable[d]**	**1**	**1-5**	**1**	**1-5**	**1-5**	**1-5**	**1-5**	**1-5**
Visit window (days)[e]		**–**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**–**	**±5**
Laboratory												
Urine pregnancy test[n]				X	X	X	X	X	X	X	X	X
Serum baricitinib concentration[o]				X	X	X	X	X	X	X		
Pulmonary function tests (SAVI patients only)[p]		X		X	X	X	X	X	X	X	X	

Abbreviations and footnotes on next page.

Abbreviations: ET = early termination; JDM = juvenile dermatomyositis; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibiody; HBsAb = hepatitis B surface antibody; HIV = human immunodeficiency virus; SAVI = STING-associated vasculopathy with onset during infancy.

a Early termination visit is required if early termination occurs.
b Visits occur at approximately 4-week intervals during Weeks 16 through 52 (including both required and optional visits)
c Visits occur at approximately 12-week intervals during Weeks 60 through 288.
d Visit 2 encompasses the initial dosing period and can vary in time depending on whether the patient progresses through the first and second dose escalation during this period. Four days is the minimum time.
e Every effort should be made to schedule patient visits within the allowable visit window; however, if a patient visit is scheduled outside the visit window, it will not be considered a protocol violation.
f If results are available from testing within 1 month, then the patient will not have to be retested.
g If a chest x-ray has not been performed in the 6 months prior to screening visit.
h Juvenile dermatomyositis patients only.
i At least 2 weeks of diary scores are required prior to beginning investigational product.
j Each time study dose is adjusted during Visit 2, this eCRF will be completed.
k See dose escalation schedule (Table JAGA.7.1 of the Protocol). Each time study dose is adjusted, this eCRF will be completed. Collect samples for chemistry, hematology, and urinalysis 2 weeks after final dose increase. Collect pharmacokinetic samples as described in Section 10.3.2 of the Protocol.
l Collect prior to each dose escalation. Investigator will review to ensure dose escalation is appropriate. Collect prior to the last dose given at Visit 2.
m If results are available from testing within the previous 3 months, then the patient will not have to be retested.
n 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 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
o Baricitinib concentration samples will be collected as described in Section 10.3.2 of the Protocol. Samples will be collected after Visit 2 only if patient has a dose escalation (see Table JAGA.7.1 of the Protocol).
p Pulmonary function tests are required for SAVI patients only. Pulmonary function tests may include vital signs, pulse oximetry, imaging, and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide. During the dose escalation period, pulmonary function will be assessed and affirmed to be stable before a patient's baricitinib dose is increased.
q These required visits may be performed at the investigative site or as a telephone visit. If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Appendix 2 (SAP).
r Optional visits may be performed at the investigative site or as a telephone visit, but will not be considered a protocol violation if not performed. If a telephone visit is performed, lab samples should be obtained locally.

Appendix 2. Protocol I4V-MC-JAGA Clinical Laboratory Tests

Clinical Laboratory Tests (Protocol JAGA [r])

Hematology[a,b,c]	**Serum Chemistry**[a,b]
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin[c]
Mean cell volume (MCV)	Direct bilirubin[c]
Mean cell hemoglobin concentration (MCHC)	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT/SGPT)[c]
Reticulocyte	Aspartate aminotransferase (AST/SGOT)[c]
Absolute counts of:	Blood urea nitrogen (BUN)[c]
Neutrophils, segmented	Creatinine[c]
Neutrophils, juvenile (bands)	Calcium
Lymphocytes	Glucose
Monocytes	Albumin
Eosinophils	Total protein
Basophils	Creatine phosphokinase (CPK)
Platelets	Uric acid
Cell Morphology	Gamma glutamyl transferase (GGT)
	Aldolase[d]
Lipid[e]	
Total cholesterol (TC)	
Low-density lipoprotein (LDL)	
High-density lipoprotein (HDL)	**Other Tests**[a]
Triglycerides	Hepatitis B Surface antigen (HBsAg)[g]
	Anti-Hepatitis B Core antibody (HBcAb)[g]
Urinalysis[a,b,f]	Hepatitis B Surface antibody (HBsAb)[g]
Color	Hepatitis B Virus DNA[g]
Specific gravity	Human immunodeficiency virus (HIV)[g]
pH	Hepatitis C antibody[h]
Protein	Thyroid-stimulating hormone (TSH)[g]
Glucose	Thyroxine (T4)[g]
Ketones	Pregnancy Test[i]
Bilirubin	QuantiFERON®-TB Gold[g,j]
Urobilinogen	Baricitinib serum concentration
Blood	
Leukocyte esterase	
Nitrite	

Abbreviations: PPD = purified protein derivative; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis; WBC = white blood cells.

Footnotes on next page.

a Assayed by local clinical laboratory.
b Unscheduled blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator.
c If a telephone visit is performed, lab samples should be obtained locally and the required labs to be reported are: total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, and all hematology as listed in Attachment 2 of the Protocol.
d Perform if inflammatory myositis is present.
e Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to test.
f Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.
g Test required at Visit 1 only to determine eligibility of patient for the study.
h A positive hepatitis C antibody result will be confirmed with a positive hepatitis C virus result.
i For all women of childbearing potential, a serum pregnancy test will be performed at Visit 1 and a urine pregnancy test (local laboratory) will be performed at Visit 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
j The QuantiFERON®-TB Gold 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. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

Appendix 3. CANDLE/CANDLE-Related Diary, SAVI Diary, and JDM Diary

CANDLE Diary

Number of days since last clinic visit: **Patient Initials: _____** **Patient #_____** **Month/Year of diary: _____**

_____

• If you are taking JAGA, please check appropriate box named study drug with a √ after each time you administer the drug

• Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.

• Score each symptom based on the scoring description provided above each symptom column

0 = No fever	**0** = No rash	**0** = No pain	**0** = No headache	**0** = No fatigue
1 = Fever without impact on daily activity	**1** = Rash barely present	**1** = Mild pain not requiring medication, no limping	**1** = Mild headache not requiring medication or any adjustments of daily activities	**1** = Mild fatigue, no functional impact
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	**2** = Rash covering 10% of body surface area	**2** = Pain requiring medication or leading to limping or other mild functional impact	**2** = Headache requiring medication or having mild functional impact	**2** = Moderate fatigue with mild functional impact
3 = Fever requiring medication with significant impact on daily activities (missing school, listlesness)	**3** = Rash covering more than 30% of body surface area	**3** = Pain requiring medication or having a severe functional impact	**3** = Headache requiring medication and having a severe functional impact	**3** = Severe fatigue with a severe functional impact
4 = Fever forcing the patient to be bedridden	**4** = Worst rash ever or covering over 30% of body surface area or hurting or stinging	**4** = Severe pain, child refusing to walk, or staying in bed most of the time	**4** = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	**4** = Severe fatigue resulting in patient staying in bed most of the time

Day	Date	JAGA Dose Given	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Headache	Fatigue	Dose of Steriods
1									
2									
3									
4									
5									
6									
7									

8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
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Name and Relationship of Person completing this form:
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Signature:
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Reviewer Name

Name:_____ Reviewer Signature: _____ Date Reviewed: _____

SAVI Diary

Number of days since last clinic visit: _____ Patient Initials: _____ Month/Year of diary: _____

• If you are taking JAGA, please check appropriate box named study drug with a √ after each time you administer the drug

• Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.

• Score each symptom based on the scoring description provided above each symptom column

0 = No fever	**0** = No rash	**0** = No pain	**0** = No fatigue	**0** = No breathing problems	**0** = No ulcers
1 = Fever without impact on daily activity	**1** = Rash barely present	**1** = Mild pain not requiring medication, no limping	**1** = Mild fatigue, no functional impact	**1** = Mild breathing problems / rapid breathing / coughing, no functional impact	**1** = Few ulcers, only in 1 location and/or no drainage, no ischemia
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	**2** = Rash covering 10% of body surface area; brighter pink to red.	**2** = Pain requiring medication or leading to limping or other mild functional impact	**2** = Moderate fatigue with mild functional impact	**2** = Moderate breathing problems / rapid breathing / coughing with mild functional impact	**2** = Ulcers in more than 1 location and/or with some drainage, no ischemia
3 = Fever requiring medication with significant impact on daily activities (missing school, listlesness)	**3** = Rash covering more than 30% of body surface area; generally red.	**3** = Pain requiring medication or having a severe functional impact	**3** = Severe fatigue with a severe functional impact	**3** = Severe breathing problems / rapid breathing / coughing with a severe functional impact	**3** = Ulcers in multiple locations and/or significant drainage, and/or any ischemia
4 = Fever forcing the patient to be bedridden	**4** = Worst rash ever or covering over 30% of body surface area or hurting or stinging	**4** = Severe pain, child refusing to walk, or staying in bed most of the time	**4** = Severe fatigue resulting in patient staying in bed most of the time	**4** = Severe breathing problems / rapid breathing / coughing which result in patient staying	**4** = Severe ulcers / ischemic lesions in multiple locations

								in bed most of the time		

Day	Date	JAGA Dose Given	A.M. Temp	Fever	Rash	Musculo-skeletal Pain	Fatigue	Respiratory/ Breathing Symptoms	Ulcers / Ischemic lesions	Dose of Steriods
1										
2										
3										
4										
5										
6										
7										
8										
9										
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11										
12										
13										
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Name and Relationship of Person completing this form:
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Signature:
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Reviewer Name

Name:_____ Reviewer Signature: _____ Date Reviewed: _____

JDM Diary

Date of last clinic visit: ____ Study #: 12-AR-8001 / JAGA Subject # _____ Month/Year of this diary page:_____

- Measure the temperature in the armpit before administering study drug (if taking) or each morning between 7 and 10 am.
- Score each symptom based on the scoring description provided above each symptom column

0 = No fever	**0** = No rash	**0** = No pain	**0** = No headache	**0** = No fatigue	0 = No muscle weakness
1 = Fever without impact on daily activity	**1** = Rash barely present	**1** = Mild pain not requiring medication, no limping	**1** = Mild headache not requiring medication or any adjustments of daily activities	**1** = Mild fatigue, no functional impact	1 = Mild weakness
2 = Fever requiring fever-reducing medication or with mild impact on daily actitivity	**2** = Rash generally brighter pink to red	**2** = Pain requiring medication or leading to limping or other mild functional impact	**2** = Headache requiring medication or having mild functional impact	**2** = Moderate fatigue with mild functional impact	2 = Moderate weakness

					3 = Fever requiring medication with significant impact on daily activities (missing school, listlessness)	**3** = Rash generally bright red	**3** = Pain requiring medication or having a severe functional impact	**3** = Headache requiring medication and having a severe functional impact	**3** = Severe fatigue with a severe functional impact	3 = Severe weakness		
					4 = Fever forcing the patient to be bedridden	**4** = Worst rash ever	**4** = Severe pain, child refusing to walk, or staying in bed most of the time	**4** = Severe headache resulting in patient staying in bed most of the day or lying down due to headache	**4** = Severe fatigue resulting in patient staying in bed most of the time	4 = Extremely severe weakness		**Who completed the diary today? S = Subject P = Parent M = Medical Staff O = Someone else (do not enter names)**
Day	**Date MM/DD/YYYY**	**Total Daily Dose JAGA mg Given**	**Missed JAGA Dose & Reason**	**A.M. Temp**	**Fever**	**Rash**	**Musculo-skeletal Pain**	**Headache**	**Fatigue**	**Weakness**	**Dose of Steriods (mg)**	
1												
2												
3												
4												
5												

6												
7												
8												
9												
10												
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NIH Study Team

Name:

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Reviewer Signature:

_____

Date Reviewed: _____

Key for scoring per symptom:

Fever	0 - 4 listed above
Rash	0 = no rash
	1 = Faint pink - involvement of a smaller area, such as joints, eyelids, and/or cheeks
	2 = Pink to red - involvement of moderate area, such as joints, face, hands, and arms, neck, and/or shoulders
	3 = Bright red - often with more extenstive involvement of meoderate area, such as joints, face, neck & shoulders, hands & arms, lower extremities, & possibly trunk or buttocks
	4 = Worst - Extremely bright red & often with itchiness, scratching, or with secondary changes of blisters, scabs or open sores, generally extensive involvement, including above areas and trunk or buttocks
Musculoskeletal	0 - 4 listed above
Headache	0 - 4 listed above
Fatigue	0 - 4 listed above
Weakness	0 = No weakness - Strong in all muscle groups & have no problems with their muscle strength or ability to do things compared to their peers
	1 = Mild Weakness - Almost normal strength in all muscles & can do almost everything with their muscles that their peers can do with minimal/mild problems
	2 = Moderate Weakness - Their muscles are somewhat weak; can do things with their muscles, but using their muscles for many things is hard for them)
	3 = Severe Weakness - Their mucles are very weak & using their mucles for most things is hard for them; they need assistance with some things)

	4 = Extremely Severe Weakness - Their muscles are extremely weak & using their muscles for everything is hard for them; they need assistance with most things)

Appendix 4. National Institutes of Health (NIH) Natural History Protocol

All patients treated at the NIH are enrolled in an observational study entitled "Studies of the Natural History, Pathogenesis, and Outcome of Autoinflammatory Diseases (NOMID/CAPS, DIRA, CANDLE, SAVI, CRMO, Still's Disease, Behcet's Disease, and Other Undifferentiated Autoinflammatory Diseases)," hereafter referred to as the Natural History Protocol (NCT00059748). The NIH operates this Natural History Protocol in order to study the signs and symptoms and to gather more information about the cause and courses of these autoinflammatory diseases. All patients being treated in JAGA at NIH are also enrolled in the Natural History Protocol. Some additional efficacy data associated with baricitinib treatment are available through the Natural History Protocol including laboratory data (eg. C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], interferon signature), additional assessments (Physician's Global Assessment of Disease Activity [PGA], Pain Global Assessment, Childhood Health Assessment Questionnaire [CHAQ], Pediatric Quality of Life Inventory [PedsQL]), and photographic documentation of treatment responses. The Natural History Protocol provides the appropriate patient consent to allow sharing of data collected in the protocol with Lilly and will be used to supplement JAGA data and provide further evidence of efficacy.

Laboratory results, photographs, and results at each visit from the PGA, Pain Global Assessment, CHAQ, and PedsQL will be transferred from NIH to Lilly. By-patient listings of laboratory results and additional assessments (summary score and change from baseline for the PGA, Pain Global Assessment, CHAQ, and PedsQL) will be provided.

The following laboratory results and assessments will be transferred from NIH to Lilly:

- ESR (first result)
- ESR (second result, if any)
- CRP (first result)
- CRP (second result, if any)
- LDH
- Ferritin
- Iron
- Transferrin
- % Saturation
- Aldolase
- Anti-Nuclear Antibody (ANA)
- Serum Osteocalcin
- Thyroid Stimulating Hormone (TSH)
- Thyroxine, Free (T4)
- Erythropoietin
- Cystatin C
- Protein Creatinine Ratio, Urine

- Urine WBC
- Urine RBC
- CD3#
- CD3%
- CD4/CD3#
- CD4/CD3%
- CD8/CD3#
- CD8/CD3%
- NK#
- NK%
- CD19#
- CD19%
- IgG
- IgA
- IgM
- IgE
- Abdominal Girth
- Interferon Signature

Physician Global Assessment of Disease Activity [PGA]:

The investigator will be asked to give an overall assessment of the severity of the subject's current RA activity using a 100-mm horizontal visual analog scale (VAS), where the left end (0) represents no disease activity and the right end (100) represents extremely active disease.

Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick.

Pain Global Assessment:

Subjects will be asked to give an overall assessment of their pain severity using a 100-mm horizontal VAS where the left end (0) represents no pain and the right end (100) represents extreme pain.

Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick.

Childhood Health Assessment Questionnaire [CHAQ]:

The Childhood Health Assessment Questionnaire (CHAQ) assesses functional health status in children aged 6 months to 18 years. The 30- item CHAQ captures 8 functional areas (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities). The CHAQ is either parent or self-administered with recall "Over the Past week". Items are scored on a 4-point scale

ranging from 0 “Without Any Difficulty”, 1 “With Some Difficulty”, 2 “With Much Difficulty”, 3 “Unable To Do” or “Not Applicable” with lower scores indicating better functioning. The highest score for any component question determines the score for that category. If a component question is left blank or the response is too ambiguous to assign a score, then the score for that category is determined by the remaining completed question(s). If all component questions are blank, then the category is left blank. The CHAQ disability index (DI) is calculated by adding the scores for each of the categories and dividing by the number of categories answered. This gives a score in the 0-3.0 range. Only the total score for the CHAQ (CHAQ DI) was transferred from NIH to Lilly, and so it is assumed that the score was calculated correctly by NIH.

Pediatric Quality of Life Inventory [PedsQL]:

The Pediatric Quality of Life Inventory (PedsQL) is a modular instrument designed to measure health-related quality of life (HRQoL) in children and adolescents aged 2-18 years. The 23-item PedsQL Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL disease-specific modules. The PedsQL captures HRQoL domains including physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). Items are scored using a 5-point Likert scale from 0 (Never) to 4 (Almost always) where higher scores indicate better HRQoL. If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. Only the total score for the PedsQL was transferred from NIH to Lilly, and so it is assumed that the score was calculated correctly by NIH. The PedsQL total score is the sum of all of the items divided by the number of items answered on all the scales.

Leo Document ID = c18095b9-1a25-4f5b-90e9-86db7d2d22d0

Approver: PPD
Approval Date & Time: 29-Apr-2016 19:12:45 GMT
Signature meaning: Approved

SUPPLEMENTAL STATISTICAL ANALYSIS PLAN: COMPASSIONATE USE TREATMENT I4V-MC-JAGA: TREATMENT OF CONDITIONS EXPECTED TO BENEFIT FROM JAK 1/2 INHIBITION: AICARDI GOUTIERES SYNDROME

This supplemental analysis plan was provided to the sponsor on October 16, 2019; the redacted form of this supplemental analysis plan was formatted on April 29, 2020.

Study I4V-MC-JAGA is an open-label compassionate use treatment program to provide baricitinib to patients with conditions expected to benefit from JAK inhibition. Patients will receive an initial dose based on their weight class and disease type that may be escalated to determine a tolerable dose. Patients may be dosed for up to 288 weeks. It is anticipated that up to 35 patients may be treated with baricitinib in an individualized manner. The treatment guidelines contained herein are for compassionate use only. All efficacy analyses for on neurologic function were designed after the trial began.

The primary purpose of this SAP is to describe the handling of the additional data collected outside of the JAGA protocol, as part of the CHOP study. The analyses in this SAP will be limited to patients with AGS.

1.1 Natural History of AGS (Supplemental SAP)

Demonstration of disease trajectory in non-baricitinib treated patients, using data from the AGS natural history study (Supp SAP).

1.1.1.1 Populations (Supplemental SAP)

- Supplemental JAGA Efficacy Population: this set will include AGS enrolled patients at the CHOP Site who have received at least one dose of baricitinib. Pre-treatment data for this population will also be included.
- Non-JAGA AGS Natural History Population: this set will include all enrolled mutation positive AGS patients from the CHOP site who did not receive baricitinib.

Kaplan-Meier curves (with 95% confidence bands) will be used to illustrate the disease trajectory in AGS patients where the time to reach developmental milestones will be plotted (as per Adang et al[1], Figures 2-5). This analyses will be performed to underscore the disease burden in AGS patients. Patient results for the GMFCS, MACS, CFSCS scales will be summarized across patients, by age group (<1, 1, 2, 3 years old etc.), to illustrate level of functioning for this non-treated cohort using these standard functional scales.[1-3] The AGS scale score will be plotted, per patient, across age (months, years), where time is negative prior to AGS diagnosis and positive after AGS diagnosis, to show pre- and post-AGS clinical presentation in non-treated patients.[2]

1.2 Parameters (Supplemental SAP)

Parameters collected outside of the JAGA protocol, as part of the CHOP studies, with the exception of demographic and diary data.

1.3 Statistical Analysis (Supplement SAP)

Summary statistical analyses will be reported (i.e. N, means, standard deviations, medians, minimums and maximums and the numbers of observations) from time periods of interest. Input data for the summary statistics will be the patient average for that time period/parameter, irrespective of number of visits or values. The rationale is that using patient averages reduces the impact of outlier single values while also capturing all data available.

Appropriate statistical tests will be done for the key variables of interest, see below. The daily diary score will be the daily sum of the symptom scores for the AGS diaries, the daily diary score will remain the average of the daily symptom scores for the CANDLE and SAVI diaries.

1.3.1 The time periods of interest for the Supplemental JAGA Efficacy Population (Supplemental SAP)

1. Baseline: up to 2 weeks prior to first dose.
2. Stable Dose: the last 6 months (180 days) on stable dose, that is, the dose did not change during this period. This time period (start MM/DD/YYYY - end MM/DD/YYYY) will be determined, per patient, by the research teams and applied to the data.
    a. Rationale: (i) as dose escalation varied across patients, data collected prior to the stable dose period are confounded by dose, (ii) as duration on stable dose varied across patients the same duration (ie. 6 months) is used and, (iii) for patients on stable dose for >6 months, the last 6 months will most accurately represent the long term efficacy of the drug.
3. Last Observation (patient's last non-missing post-baseline measurement during the treatment period, single time point).
    a. for diary data, this will be the average daily diary score post the preceding visit
4. Change: Change from Baseline to Stable Dose. *Paired t-test or Wilcoxon, depending on normality; Shapiro-Wilk test on model residuals, alpha = 0.001*
5. Change: Change from Baseline to Last Observation. *Paired t-test or Wilcoxon, depending on normality; Shapiro-Wilk test on model residuals, alpha = 0.001*
6. Other time periods that would be included as requested by the site or sponsor

1.3.2 The time period of interest for the Non-JAGA AGS Natural History Population (Supplemental SAP)

Disease Trajectory: Time to reach developmental milestones for milestones achieved. Time to lose developmental milestones for milestones achieved then lost using *Kaplan-Meier plots.*

1. Average of last 6 months on study for never treated AGS. *Comparison with time point #3 above for treated AGS by ANCOVA where covariates will be demographic and other patient related factors e.g. age, gender etc. Non-normally distributed data (Shapiro-Wilk test on model residuals, alpha = 0.001) may be log or rank transformed prior to analyses.*

   In addition to these, other statistical methods to demonstrate treatment efficacy in the baricitinib treated AGS patients with reference to (1) non-treated natural history cohort (2) pre-treatment data from baricitinib treated patients is being evaluated.

Summary statistical analyses for the above time periods will be reported by disease (CANDLE, SAVI, and AGS) and potentially by other subgroups as requested by the research teams (NIH and CHOP). Other statistical and non-statistical comparisons may be included to support the submission.

The complete data set, including values from the time periods of interest and those outside the time periods of interest, will be reported as data listings. Patient case studies and dose escalations will be reported in the JAGA CSR.

1.4 Demonstration of efficacy (Supplemental SAP)

Demonstration of efficacy in baricitinib treated patients, using data from JAGA, pre-treatment JAGA data and AGS natural history data.

1.4.1 Clinical endpoint: AGS scale (Supplemental SAP)

Using non-treated, pre-treated and post-treatment data, the AGS scale measurements for the non-treated AGS natural history population and treated AGS patients (JAGA) will be compared using propensity scoring.[4] A logistic regression model will be performed across all time-points combined, with treatment (1 = treated, 0 = not-treated) as the outcome variable. The logistic model will include the following covariates: age at baseline, age of onset of disease, an indicator variable for microcephaly at baseline, grouped-genotype (via indicator variables for RNASEH2B and SAMHD1/ADAR/IFIH1 combined, with TREX1 as the reference; as per Adang et al[1]) and AGS at the previous visit. This logistic model will be used to obtain predicted probabilities of treatment for all time-points combined. The predicted probabilities will then be used as propensity scores for treatment for each patient at each evaluation. A GEE (General Estimating Equation) model will then be constructed that will include AGS score as the outcome variable and the following covariates: (i) prior AGS Scale as a variable and (ii) an indicator variable for treatment and, (iii) the propensity score. An identity correlation structure with robust standard errors will be used to account for correlation within AGS measurements on the same patient. The significance of each factor,

including treatment, will be tested in the GEE model where a significant effect of treatment (p<0.05) will support a finding of efficacy.

1.4.2 Supportive analyses (Supplemental SAP)

Using non-treated, pre-treated and post-treatment data, Longitudinal GEE model in an unadjusted analysis that compares average (patient level) AGS values post-treatment to average values pre-treatment (including patients who were never treated). In the GEE model, the patient level outcomes will be the mean AGS scale pre-treatment and the mean AGS score post-treatment. Non-treated patients will therefore have one value of the outcome variable in this analysis. A significant effect of treatment (p<0.05) in the GEE model will support a finding of efficacy.

Graphical displays of overlaid individual level plots of AGS versus time, where time within patients is negative prior to treatment and positive after treatment. Application of the approach in Section 15.4 of Fitzmaurice et al [5] that fits a GEE model that includes time within patients, an indicator variable for treatment and a time by treatment interaction term. The GEE models also included demographic variables that include age at start of treatment (versus accounting for covariates via propensity as in Keogh et al [4]. The GEE models accounted for intra-subject correlation of measurements with an AR(1) correlation structure.

Analysis of Covariance Model (ANCOVA) will be used to compare the AGS scale results between the two cohorts (treated and non-treated) at the last observation (without inter-current illness or infection) and will including the following covariates: age at baseline, age of onset of disease, disease duration, an indicator variable for microcephaly, grouped-genotype (via indicator variables for RNASEH2B and SAMHD1/ADAR/IFIH1 combined, with TREX1 as the reference; as per Adang et al[1]. A significant effect of treatment (p<0.05) will support a finding of efficacy.

1. Adang L, Gavazzi F, De Simone M, et al. Developmental outcomes of Aicardi Goutières Syndrome. Journal of child neurology 2019.
2. Adang LA, Gavazzi F, Jawad AF, et al. Development of a neurologic severity scale for Aicardi Goutieres Syndrome. Molecular genetics and metabolism 2020.
3. Rice G, Patrick T, Parmar R, et al. Clinical and molecular phenotype of Aicardi-Goutieres syndrome. American journal of human genetics 2007;81:713-25.
4. Keogh RH, Daniel RM, VanderWeele TJ, Vansteelandt S. Analysis of Longitudinal Studies With Repeated Outcome Measures: Adjusting for Time-Dependent Confounding Using Conventional Methods. American journal of epidemiology 2018;187:1085-92.
5. Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis: Wiley-Interscience; 2004.

Changes to the natural history protocol "The Myelin Disorders Biorepository Project and Global Leukodystrophy Initiative Clinical Trials Network" at the Children's Hospital of Philadelphia

This protocol was originally submitted to the IRB at the Children's National Medical Center ~ 2003. The earliest electronic version of this protocol is from 2005. This natural history protocol has continued to evolve and was transferred in the fall of 2016 to the Children's Hospital of Philadelphia. For the purposes of review of this study, the protocol that was in place when the first patients in this report were started on baricitinib, approved in November 2015, is included as the "first" version of this protocol, although additional versions of this protocol between 2005-2016 are available upon request.

Also provided below is a summary of all amendments to this protocol since 2015. All other amendments were personnel amendments that did not modify the protocol.

Date	Protocol	Comments
9/23/2019	MBDP Protocol AMD45	This amendment involves the addition of Baylor College of Medicine, Children's Hospital Colorado, Mass General Hospital, & Stanford University as relying institutions, adds the CPCHILD questionnaire, updates the Outcome Measures and Assessments spreadsheet, and includes minor administrative edits.
6/24/2019	MBDP Protocol AMD42	This amendment involves the submission of two NIH grants and updating the study title. All study materials have been updated.
6/13/2019	MBDP Protocol AMD32	This amendment includes the addition of University of Utah, Kennedy Krieger Institute, and the University of Pennsylvania as relying sites; adding assessments/questionnaires and an optional use of photographs or recordings (audio or video) for research. The consent forms were updated accordingly.
1/5/2019	MBDP Protocol AMD27	This amendment involves IRB review and execution of a Authorization Agreement (SMART IRB) with Children's National Medical Center. CHOP is now the Reviewing IRB for this institution. Investigators at this site are now approved to conduct human subjects research for the study (pending any local institutional requirements). This amendment also involves expanding the data transfer plan to reflect that the PI may share a limited data set with entities funding this research. Revised informed consent documents were also approved with this amendment.
5/24/2018	MBDP Protocol AMD23	This amendment involves IRB review and execution of an Authorization Agreement for Emory University. CHOP is now the Reviewing IRB for this institution. Investigators at this site are now approved to conduct human subjects research for the study (pending any local institutional requirements).
4/12/2018	MBDP Protocol AMD20 Revision	This amendment involves modifying all study materials to allow enrollment of subjects with disorders affecting the white matter of the brain, other than leukodystrophy, include an additional aim to connect subjects with other relevant research or clinical programs and make minor administrative edits and clarifications. Additionally, a survey has been created for subjects who undergo whole genome sequencing as part of clinical care and the Nemours Foundation has been added as a participating site for which CHOP will serve as the IRB of record. Lastly, this amendment includes modifications to the data transfer plan.
1/30/2018	MBDP Protocol AMD19 Revision	This amendment involves expanding the consent process to reflect that the short form consent process may be completed over the telephone utilizing a telephone interpretation service. Written consent will still be obtained from non-English speaking subjects, however documentation of the interpreter's participation in the discussion may be made by the study team in a note to file in limited circumstances where it is not feasible to obtain the written signature of the interpreter. These changes do not affect the IRB's previous risk-benefit assessment of the study.

10/30/2017	MBDP Protocol AMD13 Revision	This amendment clarifies that the study will only cover nursing/phlebotomy fees for samples collected at CHOP. If a subject chooses to have samples collected at an off-site location, the study team will provide a sample collection kit and pre-paid shipping materials but will not pay for other costs. Shire Pharmaceuticals was added as a secondary funder. The consent forms were updated to reflect the NIH's current policy on Certificates of Confidentiality.
4/17/2017	MBDP Protocol AMD8	This amendment involves IRB review and execution of Authorization Agreements for The University of Wisconsin -Madison. CHOP is now the Reviewing IRB for this institution. Investigators at this site are now approved to conduct human subjects research for the study (pending any local institutional requirements). Additional administrative edits have been made to the study materials.
2/18/2017	MBDP Protocol AMD2	This amendment includes changes to sample collection procedures. Extra samples for research purposes will now be collected, when possible, from subjects who undergo clinically required lumbar puncture, blood draws, or urine collection. Language describing the NeuroBANK database and related Global Unique Identified (GUID) has been updated for accuracy.
12/19/2016	MBDP Protocol Initial Submission Acceptance at CHOP	
11/9/2015	Last protocol approved at Children’s National Medical Center	It is under this version of the Myelin Disorders Bioregistry project that the first 3 individuals included in this study were enrolled prior to the transfer of this protocol to CHOP.

Title: **The Myelin Disorders Biorepository Project and Global Leukodystrophy Initiative Clinical Trials Network**

Short Title: Myelin Disorders Biorepository Project (MDBP)

eIRB No.: 14-011236

Protocol: December 2016

Amendment 1: December 2016 (Withdrawn)
Amendment 2: February 2017 (Full Amd.)
Amendment 3: January 2017 (Staff Change)
Amendment 4: February 2017 (Staff Change)
Amendment 5: February 2017 (Staff Change)
Amendment 6: March 2017 (Withdrawn)
Amendment 7: March 2017 (Staff Change)
Amendment 8: June 2017 (Full Amd.)
Amendment 9: June 2017 (Staff Change)
Amendment 10: June 2017 (Staff Change)
Amendment 11: August 2017 (Withdrawn)
Amendment 12: September 2017 (Staff Change)
Amendment 13: November 2017 (Full Amd.)
Amendment 14: October 2017 (Staff Change)
Amendment 15: December 2017 (Staff Change)
Amendment 16: December 2017 (Full Amd.)
Amendment 17: December 2017 (Staff Change)
Amendment 18: January 2018 (Staff Change)
Amendment 19: February 2018 (Full Amd.)
Amendment 20: April 2018 (Full Amd.)
Amendment 21: February 2018 (Staff Change)
Amendment 22: April 2018 (Staff Change)
Amendment 23: June 2018 (Full Amd.)
Amendment 24: June 2018 (Withdrawn)
Amendment 25: August 2018 (Staff Change)
Amendment 26: August 2018 (Staff Change)
Amendment 27: January 2019 (Full Amd.)
Amendment 28: September 2018 (Staff Change)
Amendment 29: October 2018 (Staff Change)
Amendment 30: October 2018 (Staff Change)
Amendment 31: February 2019 (Staff Change)
Amendment 32: TBD (Full Amd.)
Amendment 33: February 2019 (Staff Change)
Amendment 34: March 2019 (Staff Change)
Amendment 35: March 2019 (Staff Change)
Amendment 36: April 2019 (Staff Change)
Amendment 37: April 2019 (Staff Change)
Amendment 38: May 2019 (Staff Change)
Amendment 39: May 2019 (Staff Change)
Amendment 40: June 2019 (Staff Change)
Amendment 41: June 2019 (Staff Change)
Amendment 42: June 2019 (Full Amd.)
Amendment 43: June 2019 (Staff Change)
Amendment 44: July 2019 (Staff Change)
Amendment 45 TBD (Full Amd.)
Amendment 46: September 2019 (Staff Change)

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TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS OF TERMS

°C	Degrees Centigrade
2-DE	Two-dimensional Gel Electrophoresis
AE	Adverse Event
CMV	Cytomegalovirus
CSF	Cerebrospinal Fluid
CLIA	Clinical Laboratory Improvement Amendments
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
iPSCs	Induced Pluripotent Stem Cells
IRB	Institutional Review Board
GCMS	Gas Chromatography - Mass Spectrometry
GUID	Global Unique Identifier
LCMS	Liquid Chromatography - Mass Spectrometry
MDBP	Myelin Disorders Biorepository Project
MRI	Magnetic Resonance Imaging
PCR	Polymerase Chain Reaction
PHI	Protected Health Information
PI	Principal Investigator
RNA	Ribonucleic Acid
RT-PCR	Reverse-transcription Polymerase Chain Reaction
SAE	Serious Adverse Event

ABSTRACT

Context/Background. Genetic white matter disorders (leukodystrophies) (Vanderver et al., 2015) are estimated to have an incidence of approximately 1:7000 live births. More than a third of these patients never achieve a molecular classification, and many of these disorders lack significant knowledge on molecular mechanisms and natural history. This biorepository approach proposes to characterize these disorders using available clinical, genetic and molecular approaches to establish novel diagnoses, biomarkers and outcome measures for future clinical diagnostic and therapeutic approaches.

Objectives. The purpose of this study is to: (Aim 1) define novel homogeneous groups of patients with unclassified leukodystrophy and work toward finding the cause of these disorders; (Aim 2) establish disease mechanisms in selected known leukodystrophies; (Aim 3) track current care and natural history of these patients to define the longitudinal course and determinants of outcomes in these disorders; and (Aim 4) to inform subjects of future research and/or clinical programs that may be of benefit based on their individual diagnoses or lack thereof. These aims will be achieved by collecting and analyzing data and samples in a longitudinal fashion across leukodystrophies.

Study Design. The design of this study is observational.

Setting/Participants. The setting of this study will include inpatient and outpatient locations both at CHOP and outside institutions.

The number of participants may change over time in this observational study but currently a recruitment ceiling of 12000 total subjects is estimated. All case subjects will be known or suspected to have a leukodystrophy or other disorder affecting the white matter of the brain. Control subjects will be enrolled through non-affected relatives of case subjects.

Inclusion Criteria (Cases)

1. Males or females of any age
2. Suspected or confirmed diagnosis of leukodystrophy based primarily on the finding of central nervous system neuroimaging consistent with this diagnosis or on an existing diagnosis of a leukodystrophy or genetic leukoencephalopathy as defined in existing classification systems (Vanderver et al., 1993, Parikh et al., 2015, Vanderver et al., 2015).

3. Parental/guardian permission (informed consent) and if appropriate, child assent or patient consent
4. Willingness to provide clinical data, participate in standardized assessment and provide biologic samples

Exclusion Criteria (Cases)

1. Identification of a diagnosis not consistent with a genetic disorder of the white matter such as an acquired demyelinating condition (e.g. Multiple Sclerosis) or an infectious etiology prior to enrollment, with the exception of sequelae of congenital infections such as CMV
2. Inability to provide consent
3. Weight below safe range for biological sample collection (typically <3kg)

Inclusion Criteria (Controls)

1. Males or females of any age
2. Individual having a relative with a suspected/confirmed leukodystrophy
3. Parental/guardian permission (informed consent) and if appropriate, child assent or subject consent

Exclusion Criteria (Controls)

1. Weight below safe range for biological sample collection (typically <3kg)
2. Inability to provide consent

Study Interventions and Measures. Study procedures include regular and ongoing review and collection of data from of clinical medical records and imaging, biologic sampling for the purpose of research (including blood, skin/tissue biopsy materials, and saliva), biologic samples collected as part of clinical care and for which leftover samples remain after clinical testing (CSF and urine), extra research samples collected at the time of a clinically-indicated procedure, and interviews and questionnaires.

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Genetic white matter disorders (leukodystrophies)(Vanderver et al., 2015) are estimated to have an incidence of approximately 1:7000 live births (Bonkowsky et al., 2010). In the past, patients with white matter disease of unknown cause evaluated by the investigator achieved a diagnosis in fewer than 46% of cases after extensive conventional clinical testing(Vanderver et al., 2012). Even when a diagnosis is achieved, the diagnosis takes an average of eight years(Vanderver et al., 2012) and this “odyssey” results in testing charges to patients and insurers in excess of $8,000 on average per patient, including the patients who never achieve a diagnosis at all(Richards et al., 2015a, Richards et al., 2015b). With next generation approaches such as whole exome sequencing, the diagnostic efficacy is closer to 70%,(Vanderver et al., 2016) but approximately a third of individuals do not achieve a specific etiologic diagnosis. This remaining group of patients (unclassified leukodystrophy) offers the opportunity to describe novel disorders and provide improved diagnostic tools. These diagnostic challenges represent an urgent and unresolved gap in knowledge and disease characterization, as obtaining a definitive diagnosis is of paramount importance for leukodystrophy patients (Kohlschutter and Eichler, 2011).

Moreover, the mechanisms of disease in many leukodystrophies of known cause are very poorly understood: many are systemic abnormalities that manifest only testing white matter. Finally, little is known about the best symptomatic management of the many leukodystrophies without an etiologic cure and thus limited standards of care are available for the management of these patients(Van Haren et al., 2015).

The purpose of this study is to: (Aim 1) define novel homogeneous groups of patients with unclassified leukodystrophy and work toward finding the cause of these disorders; (Aim 2) assess the validity and utility of next-generation sequencing in the diagnosis of leukodystrophies; (Aim 3) establish disease mechanisms in selected known leukodystrophies; and (Aim 4) track current care and natural history of these patients to define the longitudinal course and determinants of outcomes in these disorders.

It is hoped that the present study will help clarify the nosology of the leukodystrophies and significantly advance our understanding of the pathogenesis of these diseases, the best diagnostic testing tools, and the best symptomatic management of these conditions. Due to the breadth of this approach, and the rarity of these conditions, these approaches will be carried out at multiple clinical centers with specialized expertise in the leukodystrophies.

1.2 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.
The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

2.1 Aim 1: Define Novel Homogeneous Groups of Patients with Unclassified Leukodystrophy and Work Toward Finding the Cause of These Disorders.

In patients with an unclassified leukodystrophy, the study team will collect as much information as available from existing medical records including existing clinical evaluations, neuropsychological/rehabilitation evaluations, and results from blood, urine, spinal fluid, radiological, and peripheral tissue pathological tests. This data will be evaluated to create nosologic groups amongst patients with unclassified leukodystrophy. Additionally, this aim includes the collection and long-term banking of biological samples in subjects with classified and unclassified leukodystrophies to develop a biorepository. These samples will be compared to samples collected from control subjects, either collected directly from enrolled subjects or through existing banked biological samples.

2.2 Aim 2: Assess the Validity and Utility of Next-Generation Sequencing in the Diagnosis of Leukodystrophies.

In the second aim of this project, unclassified leukodystrophy patients may undergo research-based genetic sequencing approaches including exome, genome, and RNA sequencing in conjunction with high-throughput genomics analysis to achieve novel molecular classifications. Data obtained using these research approaches will not be disclosed to subjects; any findings achieved on a research basis must be validated by subsequent confirmatory testing in a CLIA/CAP-certified laboratory prior to disclosure.

2.3 Aim 3: Establish Disease Mechanisms in Selected Known Leukodystrophies.

Specific leukodystrophies will be selected for further mechanistic study, using clinical and laboratory tools to establish increased understanding of the underlying pathophysiology. The over-riding hypothesis of this aim is that integrated

biochemical, genomic, metabolic, histologic and immunologic profiles of patients with leukodystrophy will define downstream pathway changes consistent with primary defects causing white matter disease. Appropriate controls will be used for comparison to disease related samples. Samples collected in Aim 1 will be used in these efforts.

2.4 Aim 4: Track Current Care and Natural History of These Patients to Define the Longitudinal Course and Determinants of Outcomes in these Disorders.

This aim includes maintaining a longitudinal collection of clinical data on disease presentation, progression, morbidities and the therapeutic interventions in leukodystrophy patients and related controls.

Table 1. Delineation of Clinical Versus Research Interventions Used to Obtain Data for MDBP

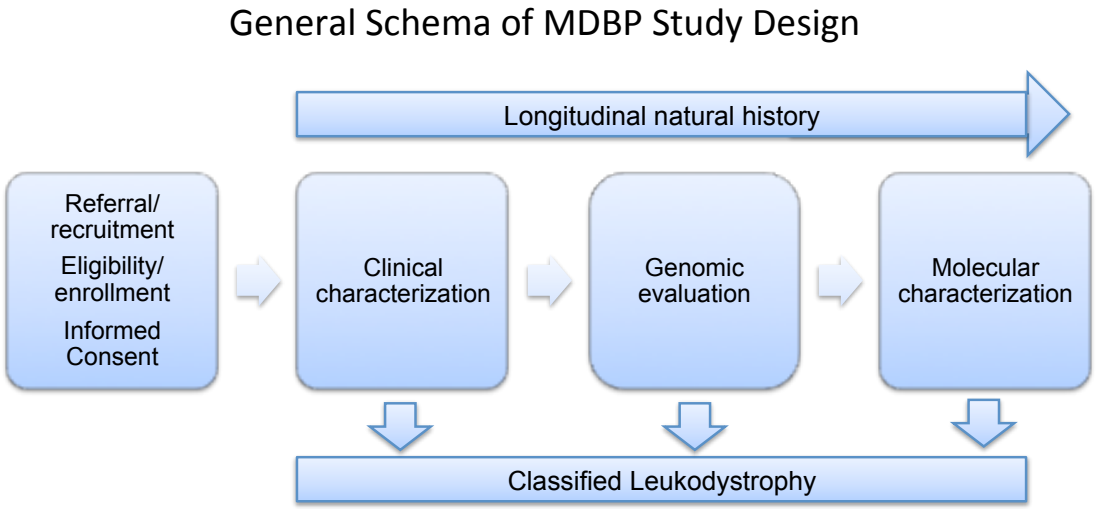
Aim	Data Collected from Standard of Care Clinical Approaches	Data Collected Explicitly for Research Purposes
1	Medical records depicting neurologic examinations, laboratory findings, and other clinical care delivered to the patient Copies of MRIs or other imaging performed as part of clinical care Leftover samples (blood, urine, biopsy tissue, CSF and others) collected during procedures done for medical care	Research only samples including: -Blood for collection of genomic DNA -skin punch (3-4mm) biopsy for the purpose of establishing iPSCs or cells for functional analysis, excluding those subjects <1 year of age and at greater risk of scarring -Leftover samples from clinical care including blood, urine, biopsy tissues, CSF and others, collected at the time of procedures done for medical care -Extra samples (blood, urine, and CSF only) collected at the time of procedures done for medical care
2	Existing genomic data performed as part of clinical sequencing, and collected for re-analysis	Generation of research WES, WGS, RNA seq or other sequencing approaches
3	None	Samples banked in 1 will be submitted to analyses including histologic, immunologic, genomic, metabolomic, proteomic, and biochemical approaches for the purpose of identifying changes that may help determine the molecular etiology or downstream changes related to the mechanism of disease
4	Medical records depicting clinical care delivered to the patient including records of hospitalizations and interventions Copies of MRIs or other imaging performed as part of clinical care	Functional outcome measures Patient reported outcome measures including quality of life surveys

2.5 Aim 5: Contact for Future Research Studies and/or Clinical Programs.

Subjects enrolled in the study may be informed of other research CHOP and non-CHOP research studies and/or clinical programs that may be of interest to them based on their specific diagnosis or lack thereof.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design (Figure 1)



The following five phases of participation are reviewed: Referral/enrollment, clinical characterization, genomic evaluation, molecular characterization, and longitudinal natural history. Case subjects may be included, depending on the characteristics of their individual disorder and research interest in all or only some parts of this general schematic.

3.2 Study Duration, Enrollment and Number of Sites

Given the need for robust longitudinal data on leukodystrophy subjects and controls, there is no specific timeframe for this study. Data collection may continue for the foreseeable future. Ongoing data collection for leukodystrophy subjects will continue as frequently as possible dependent on the clinical care schedule. Comparative control data may also be collected if possible, to enable the ongoing comparison of outcomes to cases.

The number of participants may change over time in this observational study but currently a recruitment ceiling of 12000 cases and their relatives/controls is estimated. All case subjects will be known or suspected to have a leukodystrophy or genetic leukoencephalopathy. Control subjects will be enrolled through non-affected relatives of case subjects.

While CHOP is currently the only site engaged in recruitment and enrollment of study subjects, the investigator expects an additional 10-15 additional sites to eventually join the study under IRB Reliance Agreements. Please refer to Appendix A for a current list of participating sites.

3.2.1 Duration of Study Participation

There is no strict schedule of visits for any subjects. For cases, new data collection is expected approximately every 6 months, consistent with the typical minimal interval at which a leukodystrophy patient is seen clinically. Additional data will be collected when the subject has an event complicating the leukodystrophy, such as an unexpected hospitalization (such as for an aspiration pneumonia), or an anticipated event (such as an elective surgery for a gastrostomy tube placement). Duration of the study for an individual case subject will vary depending on a specific subject's clinical care needs and whether or not s/he is being seen regularly at a participating study site. Data and samples may continue to be collected on control subjects for the purpose of ongoing comparisons between cases and controls.

Samples will be retained indefinitely, to assist in the identification of rare entities, which may present only in an exceptionally small number of individuals, and to assist in the development of biomarkers for established disorders.

3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

Other domestic study sites may be added under IRB Reliance Agreements once appropriate material transfer, data use, and contractual agreements have been negotiated. Please see Appendix A for a list of active IRB Reliance Agreements with other domestic study sites.

Collaborators at international study sites will be responsible for independently submitting the appropriate regulatory documentation to their local Institutional Review Board or Ethics Committee for local review and approval.

The number of subjects may change over time in this observational study but currently a recruitment ceiling of 12000 total subjects is estimated.

3.3 Study Population

3.3.1 Inclusion Criteria: Cases

1) Males or females of any age
2) Suspected or confirmed diagnosis of leukodystrophy based primarily on the finding of central nervous system neuroimaging consistent with this diagnosis or on an existing

diagnosis of a leukodystrophy or genetic leukoencephalopathy as defined in existing classification systems (Vanderver et al., 1993, Parikh et al., 2015, Vanderver et al., 2015).
3) Parental/guardian permission (informed consent) and if appropriate, child assent or patient consent
4) Willingness to provide clinical data, participate in standardized assessment and provide biologic samples

3.3.2 Exclusion Criteria: Cases

1) Identification of a diagnosis not consistent with a genetic disorder of the white matter such as an acquired demyelinating condition (e.g. Multiple Sclerosis) or an infectious etiology prior to enrollment, with the exception of sequelae of congenital infections such as CMV
2) Inability to provide consent
3) Weight below safe range for biological sample collection (typically <3kg)

3.3.3 Inclusion Criteria: Controls

1) Males or females of any age
2) Individual having a relative with a suspected/confirmed leukodystrophy
3) Parental/guardian permission (informed consent) and if appropriate, child assent or subject consent

3.3.4 Exclusion Criteria: Controls

1) Weight below safe range for biological sample collection (typically <3kg)
2) Inability to provide consent

3.4 Study Procedures

3.4.1 Screening and Enrollment

Case subjects will be identified through various mechanisms. Initial identification will most commonly occur through the subject's clinical leukodystrophy specialist or neurologist, but the study team may also be contacted directly by a subject or the subject's caretaker and contact information/indication of interest in the study will be provided by the family via a secure database, REDCap. The study will be discussed with the prospective subject's parents and consent will be obtained. Subjects will be informed during the consent process that their medical information, including MRI imaging, will be reviewed to confirm the case subject meets the required inclusion/exclusion criteria. If a finding is made in this period that suggests that subject does not have a leukodystrophy, the family will be informed and their participation will be ended. For all

other subjects, once the initial screening period is completed, subjects will continue directly into the Observation period.

Subjects may be seen in person but may also participate remotely by forwarding their biological samples and data to the researchers for inclusion in the database and biorepository once informed consent has been obtained.

Control subjects will be identified through enrolled case subjects and will be approached for consent either in person or on the phone. Control subjects will be enrolling directly into the observational period; there are no required screening procedures though there is a possibility that the subject would be removed from the study if an underlying medical condition is discovered that would complicate comparative analyses.

3.4.2 Observational Period (Initial Visit and Follow-Up Visits)

Due to the rarity and complexity of leukodystrophies, the clinical assessment and diagnosis of these patients can be complicated and may involve testing and expertise across multiple medical specialties. This leads to a “standard of care” that is variable across providers and institutions. This can be problematic for all leukodystrophy patients, particularly those with unclassified leukodystrophies. For this reason, this study will implement a standard process for collecting medical record data from commonly shared variables and test findings to better identify common themes and trends in the treatment of these patients. Subjects will be asked provide biologic samples as described in section 4.2. Patients will also undergo standardized assessments as provided in section 4.3.

3.4.2.1 Clinical Characterization:

Detailed clinical information will be collected for enrolled leukodystrophy subjects and analyzed in a standardized, descriptive fashion to identify novel nosologic groups to identify novel disorders within the classified leukodystrophies. Medical records with relevance to understanding the proband’s genetic and medical background, including prenatal records if the mother is consented as a control subject, will be reviewed and abstracted. Subjects will provide consent for the study, which will include review of their medical records and then, if these medical records come from outside of CHOP or a subject’s local institution, will need to also sign a release of medical information form. Previous and ongoing evaluations including standard biochemical, genetic, neurophysiologic and neuroimaging studies will be reviewed.

Biological samples will also be collected from leukodystrophy subjects for analyses and long-term storage in a biorepository. The study team will make every effort to collect research samples at the time of clinically indicated testing. These samples will include urine, blood, tissue, fibroblasts or cerebrospinal fluid. If tissues are obtained for clinical diagnostic purposes (biopsies of brain,

liver, muscle for example), leftover sample not used for pathologic analyses may be banked. In cases where clinically indicated venipuncture is not occurring, blood samples may be obtained for research purposes. In some cases, the investigator may request extra research samples (blood, urine, CSF) to be collected at the time of a clinically-indicated procedure, provided that the total (research + clinical) sample amount/volume does not exceed a clinically accepted definition of "minimal risk." Saliva may be obtained for research purposes. In cases where this tissue is not available a skin punch biopsy (3-4mm) may be performed. Punch biopsies for research purposes will not be performed in individuals under a year of age or at greater risk of scarring.

Control data/samples will be collected both from the medical records, interviews, and questionnaires from healthy family members of leukodystrophy patients and from pre-existing tissue banks (fibroblast cultures, cerebrospinal fluid).

3.4.2.2 Genomic Evaluation:

Research-based genetic testing, including exome, genome, and RNA sequencing in conjunction with high-throughput genomics analysis may be performed on patient and control samples. These samples may be obtained specifically for research purposes, or as leftovers from procedures performed as part of a subject's routine clinical care. Any genetic findings achieved on a research basis must be validated by subsequent confirmatory testing in a CLIA/CAP-certified laboratory prior to being disclosed to subjects.

3.4.2.3 Molecular Characterization:

Case subjects with specific leukodystrophies will be selected for further mechanistic study, using clinical and laboratory tools to establish increased understanding of the underlying pathophysiology. In this select group, biological samples will be submitted to analyses including histologic, immunologic, genomic, metabolomic, proteomic, and biochemical approaches for the purpose of identifying changes that may help determine the molecular etiology or downstream changes related to the mechanism of disease.

3.4.2.4 Natural History:

For most leukodystrophies, the natural disease course including age at presentation, features of disease, long term complications and standard symptomatic management and their impact are unknown. This aim will review and record case subject reported outcomes as well as clinical records to create a longitudinal dataset of these features. Established functional outcome assessments (which may include as an example the Gross Motor Function Measure 88, neurocognitive function and other established tools) may be used in selected leukodystrophies. Finally, patient reported outcomes would be generated from case and control subjects in

standardized intervals, which may include quality of life questionnaires to help characterize the impact a diagnosis of leukodystrophy has on a patient and family.
A unique identifier linking the family member and their relationship to the case will be created in the study database.
De-identified control samples will also be obtained from several sources (see section 4.2).

3.5 Subject Completion/Withdrawal

Withdrawal from the study is permitted at any time and would result in removal of any identifying information from recorded databases and destruction of any biological samples collected. Withdrawal from the study will also suspend any further medical record data collection.

Samples that have been de-identified in the course of research applications will remain in the repository as it would not be possible to identify the sample for removal. Additionally, de-identified samples that have been sent to collaborators may not be able to be retrieved.

4 STUDY EVALUATIONS AND MEASUREMENTS

4.1 Medical Record Review

Elements of history and examination pertinent to the diagnosis of a leukodystrophy for case subjects will be recorded in a database. Available neuroimaging, neurophysiologic, biochemical and molecular data for individual case subjects will be reviewed and recorded (see appendices and data collection forms). Records will be requested for any biochemical and molecular studies performed as part of clinical care for case subjects and family member subjects, if relevant for comparison to the relative's case data. Data from previously performed next generation sequencing approaches will be requested for review for all subjects.

Minimal medical history information will also be collected upon occasion from family members and will be primarily targeted at elucidating better understanding of the cases' condition, based on information in their relative's medical history.

4.2 Collection of Biological Samples

Biological samples will be collected from leukodystrophy subjects and related controls/family members for analyses and long-term storage in a biorepository. If the subjects are seen at a study site, samples will be collected following local SOPs for collection of research specimens and will be done at the same time as a clinical sample collection, if possible. Subjects will not incur any costs for biological samples collected at CHOP or another participating study site; these costs will be covered fully by the principal investigator or local investigator.

If the subjects are not seen at the study site, they will be instructed to have blood collected at their local physician's office or lab, with the collected sample forwarded for processing and onward storage in the CHOP biorepository. For blood draws performed offsite, the investigator will provide subjects with a standard sample collection kit containing sample vacutainers and packaging materials, and will pay for expedited shipping of outbound materials and inbound samples. However, the investigator cannot reimburse subjects for other costs (nursing and/or phlebotomy fees, transportation costs, etc.) incurred during the off-site sample collection process.

Occasionally, the principal investigator may request collection of extra research sample at the time of a routine clinical blood draw. In such circumstances, clinical samples will be prioritized over research samples. Furthermore, the total (research + clinical) volume of sample must fall within the institution's phlebotomy guidelines for the maximum weight/age-allowable volume.

Samples will be assayed according to techniques selected among standard laboratory manipulations, including histologic, immunologic, biochemical, genomic and proteomic techniques including the following: immunohistochemistry, histochemistry, cell culture and cellular based experiments, live cell imaging, ELISA, multiplex measurements of cytokines, chemokines, and antibody arrays, GC and LCMS small molecule measurement, Gene expression profiling, RT PCR, standard sequencing, next generation sequencing, western blot, 2D gel analysis, low molecular weight proteomics, shot gun proteomics.

4.2.1 Peripheral Blood Collection

A blood sample or filter paper blood sample may be obtained for studies of genomic DNA, RNA or disease specific analytes in cases and control subjects. Additionally, serum and plasma may be banked for culture. Peripheral blood cells may be transformed as lymphoblastoid cell lines or iPSc generation. The blood draws will not exceed the NIH limits of no more than 5 ml/kg in a single day, and no more than 9.5 ml/kg over an 8-week period. Blood sampling is not expected for patients under 3kg.

4.2.2 CSF Sample Collection

Leftover cerebrospinal fluid samples will be collected in leukodystrophy subjects after clinically-mandated lumbar puncture. The investigator may request extra CSF to be collected at the time of a clinically-mandated lumbar puncture, provided that the total (research + clinical) volume of CSF collected falls within the clinical guidelines for CSF collection (see below). Any available leftover cerebrospinal fluid will be banked.

Collection of CSF samples should not exceed reasonable estimations of CSF production and replacement. Evidence suggests as well as in that in children and adults (defined in these studies as 9 years to 61 years in source documentation), CSF production is greater than 0.3ml/min or

0.02-0.05% of the total volume per minute, with a turn-over of the entire brain CSF in adults approximately 3-5 times per day. In children and adults, total CSF volume is estimated at 150 cc. Total CSF volume in a newborn is estimated to be 50 ml and to increase gradually with age to an adult volume. Thus, in an infant, CSF production is estimated at about 6-10 cc per hour and in older children about 18 cc per hour. In this investigator's previous experience on other protocols, in children 10 years and above, 15cc of CSF is commonly collected knowing that this volume will be replaced in one hour. In infants and younger children more moderate volumes are typically recommended, and the investigator has used 5 cc in infants and 10 cc in children. There are no published norms for this that the investigator is aware of but the investigator proposes:

Age of subject	Total amount of sample drawn (**including any clinical labs that need to be obtained during the same lumbar puncture)**
Neonate at least 3kg to <4 years and 15kg	5cc, no more than once in a one-week period
4 years and 15 kg to 10 years and 30 kg	10 cc, no more than once in a one-week period
≥10 years and 30kg	15 cc, no more than once in a one-week period

CSF will not be collected from family members.

4.2.3 Saliva Collection

A saliva sample may be collected from cases and related controls/family members for the specific purpose of DNA/RNA extraction.

4.2.4 Skin Punch Biopsy

In select circumstances, additional procedures may be performed in cases such as a skin punch (3-4mm) biopsy that will not require anesthesia/sedation or sutures. Fibroblasts may be collected for the express purpose of obtaining patient cells for analysis of identified candidate genes/function and or the creation of cell lines including iPSCs (induced pluripotent stem cells). If a clinically indicated skin biopsy has been performed, and banked cells exist, those specimens will be sought and obtained rather than impose a repeat skin biopsy. Punch biopsies on a research basis will not be performed in individuals under a year of age or at greater risk of scarring.

These samples will not be collected from related controls/family members.

4.2.5 Urine Collection

Urine from case subjects will be processed from leftover clinical sample collected for clinically indicated reasons, if available. The investigator may also request extra urine to be collected for research purposes at the time of a clinical visit or inpatient stay, provided that this falls within the clinically accepted guidelines for urine sample collection.

4.2.6 Additional Tissue Samples

If cases have additional clinical testing during which other tissue samples are obtained (for example a nerve, muscle, liver or brain biopsy), leftover biopsy material after clinically indicated pathologic studies are completed may be banked. We may also ask to collect previously banked filter paper blood spots (such as newborn screening samples).

4.2.7 Additional Control Samples

In addition to the samples collected above, additional control data/samples may be obtained from pre-existing tissue banks (fibroblast cultures, cerebrospinal fluid). The investigators will not be able to readily ascertain the source of these samples (e.g. de-identified, or coded samples from a collaborator [the code will not be provided]). These are outlined in the table below. If the data/samples are being provided by a data registry, biospecimen repository or other data source, the investigators will maintain documentation that either of the following is in place: (1) policies and procedures that prevent the release of identifiers; or (2) an agreement in place between the data source and the investigator stating that no identifiers will be released under any circumstances. Research on samples/data which are not readily identifiable does not constitute human subjects research. Therefore, the individuals whose not readily identifiable data/samples are included in this research will not be included in the enrollment numbers for this study and research activities using these samples/data will not be reported as part of the continuing review.

Table 3. Examples of control subjects
In the case of blood or saliva samples (consent will be sought)
Healthy family volunteers
In the case of cerebrospinal fluid (pre-existing specimens, consent will not be sought)
Pre-existing banks of cerebrospinal fluid of patients with traumatic brain injury, brain tumor, aseptic meningitis or other neurologic disorders (anonymous samples).
In the case of fibroblasts (pre-existing specimens, consent will not be sought)
Banked anonymous fibroblast cell cultures of healthy control subjects

4.3 Questionnaires, Interviews, and Standardized Assessments/Examinations

Subjects may be invited to participate in standardized functional assessments or neurological examinations performed at intervals of at least six (6) months. These assessments and

examinations will be administered by qualified clinical staff at the Children's Hospital of Philadelphia or another participating study site to establish functional outcomes. A list of commercially-available standardized assessments used in the context of this study has been included as an attachment to the IRB application. Subject will not incur any expenses by participating in these assessments.

Patient-reported outcomes may be obtained more frequently using both standardized (i.e. commercially available) and non-standardized questionnaires administered either in electronic or paper format. Questionnaires may occasionally be administered in interview form, with a qualified member of the study team conducting either an in-person or telephone interview. Subject will not incur any expenses by participating in these assessments.

4.4 Photographs, Video, and Audio Recordings

Many affected subjects have physical features or functional characteristics that reflect their diagnosis, making photographs and video recordings useful for research and teaching purposes. Consent will be obtained to request existing photographs or video recordings that demonstrate physical features or functional characteristics. These may show the subject's body or specific areas of the subject's body. Unless needed to demonstrate clinical features, study staff will attempt not to photograph or record a subject's face. New photographs or video records may also be taken in the context of optional functional assessments or visits to a participating study site.

In cases where affected subjects are seen for in-person assessments and/or examinations, study staff may obtain audio recordings of the visit to facilitate collection of data, and specifically to avoid interrupting the assessments to take paper-based notes. Audio recordings may also be obtained in the context of in-person and/or telephone interviews using IRB-approved surveys and questionnaires. These audio recordings will be stored securely and will be accessible by approved study staff only.

Unaffected subjects such as parents, siblings, extended family members, and other healthy controls may be invited to participate in in-person and/or telephone interviews. Audio recordings of such interviews may be obtained, and will be stored securely and accessed only by approved study staff only.

5 STATISTICAL CONSIDERATIONS

5.1 Statistical Methods

The bulk of data to be collected will be descriptive in nature. In order to characterize the clinical features of the different types of leukodystrophies, we will compare the various classified and unclassified leukodystrophies based on either analysis of variance or covariance for measurement outcomes or contingency table analysis or logistic regression for categorical

variables. T- of F-statistics will be used to identify statistically significant differences in the means between groups and chi square values will be used to identify statistically significant differences in the frequency of categories between groups. This analysis will help us identify those factors that are common to many or all forms of leukodystrophies and those that may be unique to the unclassified forms. We will pay particular attention in subsequent analyses to those features that are distinctive among the groups. Subsequent analyses will employ two distinct methods of data reduction, one statistical, exploratory factor analysis, and one heuristic, neural network analysis, to attempt to define subtypes based on clinical features within the unclassified group. By comparing the results of the two methods, we will be able to identify those subtypes for which there are not agreement between the different methods.

5.1.1 Sample Size and Power

The data reduction/classification steps are viewed as hypothesis generating and thus have not subjected to power analysis.

5.2 Control of Bias and Confounding

The subjects in this observational study will not assigned by a process of randomization and are therefore subject to bias. The descriptive approach to analyses and the hypothesis generating approaches will be less likely than other approaches to be significantly affected by these confounders. There is no possibility for randomization or controlled experimentation in these approaches.

6 SAFETY MANAGEMENT

6.1 Safety Evaluation

There is no formal Data Safety Monitoring Board for this study. Subjects will be continuously monitored for adverse events, excluding those anticipated in leukodystrophy patients, such as respiratory, gastrointestinal, and bone complications of these disorders (Van Haren et al., 2015). Adverse events related to study related procedures, in particular to research only procedures, would be documented and reported as detailed below. If unexpected adverse events occur, the investigator will meet with the IRB and determine if a more robust data safety plan would be beneficial to provide additional oversight over study activities.

6.2 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study. These are not anticipated in relation to the study procedures, though we expect unrelated adverse events including death to occur in these individuals due to the natural history of these disorders (Van Haren et al., 2015).

6.3 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review. Anticipated adverse events unrelated to study procedures, related to the severe natural history of these conditions (Van Haren et al., 2015), will not be reported.

7 STUDY ADMINISTRATION

7.1 Data Collection and Management

The study data will be retained in the study-specific REDCap data base at CHOP and the NeuroBANK™ database. NeuroBANK™ is a collaboration and data repository platform maintained by the Massachusetts General Hospital (MGH) Neurological Clinical Research Institute (NCRI). This platform facilitates:

1. Capture of clinical and research data from neurologic patients for individual projects in a structured and secure system;
2. Aggregating and sharing uniform, de-identified and/or anonymized datasets for secondary analyses.

Data management (DM) at NeuroBANK™ is responsible for the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with applicable sponsor and regulatory requirements. Site personnel will collect, transcribe, correct, and transmit the data onto source documents, case report forms (CRFs), and/or other forms used to report, track and record clinical research data. DM is responsible for developing, testing, and managing clinical data management activities. The NeuroBANK™ platform provides password protection. An edit checking and data clarification process will be put in place to ensure accuracy of the data. Logic and range checks as well as more sophisticated rules may be built into the eCRFs to provide immediate error checking of the data entered. The system has the capability to automatically create electronic queries for forms that contain data that are out of range, out of window, missing or not calculated correctly. The sites will only have access to the queries concerning their subjects. Identifying information about subjects will only be visible to site specific personnel. CHOP and

NeuroBANK™ personnel would additionally have access to non-identifying data for validation and monitoring of data.

For samples from healthy family members, a unique identifier linking the family member and their relationship to the proband will be created.

7.1.1 Sample Retention

Samples collected as part of this study protocol will be retained for research testing **only**, and will be de-identified as outlined in Section 7.2. Results of this testing will not be returned to participants or their families. At the principal investigator's discretion, select research findings may warrant independent clinical validation, or subsequent testing as part of a "screening mechanism" for interventional clinical trials. In such circumstances, the principal investigator may order a clinical blood draw and subsequent sample processing/storage in a CLIA-certified laboratory. Previously collected research samples will **not** be used in these circumstances.

If a participant is otherwise seen by the principal investigator in a clinical setting, the investigator may report results of clinically validated tests directly to the participant/family. Otherwise, such results will be reported to the participant/family via a designated referring provider.

All samples will be stored in dedicated freezer space using coded freezer safe label systems with barcode identification. Those samples (such as filter paper blood spots or paraffin embedded blocks or slides) able to be banked in non-refrigerated settings will be kept in a locked cabinet. Coded samples may be shared with researchers in the U.S. or other countries to perform additional research, place it into research databases, or use it to improve the design of future studies. These samples will be de-identified to the recipients but site investigators will retain a mechanism to identify the subject. Coded fibroblast samples will be sent to collaborators, for establishment and research of human induced pluripotent stem cells (iPSCs). At no point will the outside researcher/institution have access to PHI of the participants.

7.1.2 Data Sources

Data sources will include clinical notes, neuroimaging reports, laboratory evaluations and other clinical evaluations, both at CHOP and outside institutions. Original radiology studies and genomic data sets may also be used. Biorepository samples will be used. Previously collected data and samples from Children's National Health System will be used in this biorepository. Additionally, existing banks of de-identified samples may be used.

7.2 Confidentiality

All data and records generated with this study will be kept confidential in accordance with institutional policies and HIPAA requirements (as applicable). The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. For data stored in the NeuroBANK™, a Global Unique Identified (GUID) number will be used as an identifier for that subject. The GUID is an 11 Character string that is generated using an encryption technology and algorithms licensed by the NCRI from the National Institutes of Health (NIH). The GUID is generated on a secure website that utilized 128-bit Secure Socket Layer (SSL). Of note, this website is not directly linked to GLIA or NeuroBANK. The GUID is generated using an irreversible encryption algorithm – it accepts twelve identifying elements (e.g. Last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth etc), and produces a unique random generated character or string, the GUID. No identifying system is stored in the system; it is simply used to generate the GUID. If the same information is entered again at another site for example, the same GUID is returned. Identifiers will only be linked to patient names through a password-protected database, accessible only to site study personnel.

Names are maintained in a site-specific database available only to members of the study team in order to provide patients with clinically relevant information generated from this study. No identifiable data will be used for future study without first obtaining IRB approval. Any data or samples shared outside of CHOP will be done so in a coded fashion with no PHI included and with the execution of all applicable agreements (i.e. MTA). The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at CHOP) before sharing a limited dataset (dates and zip codes).

Subject photographs and video recordings will be stored in a secured shared drive maintained by Research Information Services (RIS) at CHOP. Only approved study staff will have access to these files. Investigators may occasionally with to include subject photographs or video recordings in scientific publications and presentations, respectively, in order to highlight clinical features associated with various diagnoses. Study staff will work with Research Communications at CHOP to ensure that identifying features (faces, name badges, clothing logos, etc.) are blurred out from photographs and video records, and that all PHI is redacted from recorded audio.

7.3 Regulatory and Ethical Considerations

7.3.1 Data and Safety Monitoring Plan

Procedures of this study are minimal risk and primarily related to the collection of biological samples and confidential information. The Principal Investigator and associate investigators will monitor adverse events, including collection of biologic samples and identification of genetic testing results and report these as detailed above to the IRB. If unanticipated adverse events are noted that change the risk assessment of the study or informed consent, modifications to the

study protocol and informed consent documents will be discussed with and submitted to the IRB. Adverse events related to study related procedures, in particular to research only procedures, would be documented and reported as detailed above. If unexpected adverse events occur, the investigator will meet with the IRB and determine if it would be beneficial to provide additional oversight over study activities.

7.3.2 Risk Assessment

The risks of this study are minimal and primarily related to the collection of biological samples and confidential information. Physical risks may result from the collection of blood samples specifically for the research and skin punch biopsy. Punch skin biopsies for research only will not be performed in subjects under a year of age and at greater risk of scarring.

Risks have been minimized as much as possible. Many samples will be leftover samples available after clinically indicated procedures or will be collected in tandem with clinically-performed procedures. In some cases, the investigator may request extra research samples to be collected at the time of a clinically-indicated procedure, provided that the total (research + clinical) sample amount/volume does not exceed a clinically accepted definition of “minimal risk.” Results from genetic testing will not be returned to families, though the study will collect the findings of any genetic testing done as part of the subjects’ clinical care.

As all subjects participating in this study have already received a diagnosis of leukodystrophy there is little risk of discrimination (legal or social) based on participation in this study. Finally, there is the risk of psychosocial stress by being asked to fill out patient reported outcome and quality of life surveys.

7.3.3 Potential Benefits of Study Participation

There is no intended direct benefit of participation. There is a potential for indirect benefit in developing better diagnosis, further understanding of pathogenesis and outcome markers for clinical trials. We believe that this study will result in new pathophysiologic understanding of these complex disorders, new biomarkers for difficult to diagnose entities and documentation of novel disorders. In addition, as the project evolves and clinically relevant biomarkers for specific disorders are established, validated, and published, clinically relevant results will be reported to the treating physician.

Over the history of this repository protocol, previously at Children’s National Medical Center, data collected has led to the identification of several new disorders (Rice et al., 2009, Bernard et al., 2010, Bernard et al., 2011, Tetreault et al., 2011, Rice et al., 2012, Steenweg et al., 2012, Depienne et al., 2013, Kevelam et al., 2013, Simons et al., 2013, Taft et al., 2013, Dallabona et al., 2014, Pizzino et al., 2014, Rice et al., 2014, Simons et al., 2015, Thiffault et al., 2015,

Dallabona et al., 2016, Jenkinson et al., 2016), biomarkers of disease in a number of leukodystrophies (Vanderver et al., 2005, Steenweg et al., 2010, Prust et al., 2011, Brown et al., 2012, Rice et al., 2013, Han et al., 2014, Vanderver et al., 2014, Cuadrado et al., 2015, Jany et al., 2015, La Piana et al., 2016), and two clinical trials, currently ongoing, in Aicardi Goutières Syndrome(Crow et al., 2014). Thus, we feel that although there is no intended direct benefit, there is potential for significant indirect benefit.

7.3.4 Risk-Benefit Assessment

Though there is no direct benefit to participating, it is expected that this research study will permit better understanding of leukodystrophies, which in time, is expected to result in new treatment options. Given nature of the procedures involved in participating, we feel the risk to benefit assessment is appropriate.

7.4 Recruitment and referrals

Leukodystrophy patients will be identified through various mechanisms. Initial identification will most commonly occur through the subject's clinical leukodystrophy specialist or neurologist, but specific recruitment and referrals approaches may occur and are detailed below.

7.4.1 Referrals

Patients with leukodystrophies will be referred from within a participating institution, including CHOP, or from outside collaborating institutions for inclusion in the study. Outside physicians who believe their patients are eligible will be asked to provide patients with contact information for the PI/co-PIs/Co-Investigators/study coordinator. If interested, prospective participants will contact the PI/co-PIs/Co-Investigators/study coordinator and asked to complete a survey to collect contact information and research or clinical interests. Once complete, the potential participant will be contacted by a qualified study staff member to review these interests and conduct the informed consent conversation if indicated.

Because of the nature of leukodystrophy, the community is very active in seeking any opportunities to learn more about their condition. As such, there will also be occasions when the study team is contacted directly by a subject or the subject's current clinical care provider. Additional referrals may come from word of mouth or patient advocacy groups.
Subjects may be seen in person but may also participate remotely by forwarding their biological samples and data to the researchers for inclusion in the database and biorepository. Additionally, online password protected databases, such as Redcap will be used to collect referral information prior to inclusion of consented patients in NeuroBANK.

7.4.2 Recruitment Strategy

Additional recruitment approaches may be used. Outside physicians who have submitted samples to the PI for previous studies of leukodystrophy will be contacted to inform them of the study. Patient-facing recruitment letters/flyers will be submitted for IRB review/approval prior to being distributed by study personnel at one or more participating study sites. Lab directors whose labs perform genetic testing for select genes related to leukodystrophy will be asked to provide information about this research to referring physicians (see recruitment materials). Additional web-based recruitment tools may include the research section of the CHOP Leukodystrophy Center website (http://www.chop.edu/centers-programs/leukodystrophy-center/research), the Vanderver Lab website (https://vanderverlab.research.chop.edu), the Global Leukodystrophy Initiative (GLIA) website (www.theglia.org), and a REDCap-based 'Referral Survey' allowing patients/families to express interest in research participation. Potential study candidates may also reference the ClinicalTrials.gov entry (https://clinicaltrials.gov/ct2/show/NCT03047369), which contains contact information for key study personnel.

7.5 Informed Consent/Assent and HIPAA Authorization

Informed consent will be mailed/ or emailed to prospective participants and eviewed over the phone prior to signing for participants not coming to a study site for clinical evaluation and will be completed in person by all participants coming to a study site for clinical evaluation. Patients who wish to enroll from outside a study site will be sent a separate instruction sheet for how to enroll, send samples, and how to arrange a clinic visit as appropriate. When possible, every effort will be made for this clinical evaluation to include a neurologic exam by the PI or qualified co-investigators in addition to a comprehensive chart review. When it is not possible for the PI/co-PI/Co-investigator to conduct a neurologic exam, records of previous neurologic exams will be requested in addition to other medical records.

For subjects enrolled at the institution where they receive care, subjects will be informed that their decision to participate will in no way impact the care that they receive or the access they currently have to their provider. The study will be discussed in a private room or on the telephone with sufficient time allotted for the subject to ask questions and decide whether they want to participate. The study team will make every attempt to ensure subjects understand that they are under no obligation to participate. The majority of the procedures being proposed would be done as part of the subject's clinical care, regardless of whether they choose to enroll. The study team will emphasize that the subject does not need to participate to proceed with the testing their clinician recommends. If desired, subjects will be permitted to take a copy of the consent form home for review.

Since leukodystrophies primarily affect children, many participants will be under the age of 18 at time of study enrollment. If further research is being done and the participant is noted to be near

or at the age of 18, the study team will attempt to reach out to obtain re-consent from the participant. If the participant is legally incapacitated, re-consent will be obtained from a legally authorized representative (LAR). The study team will specifically discuss with the LAR their role as the participant's representative to assess this relationship. If efforts to reach the participant are not successful (3 attempts by phone or email on separate days and separate times and hard copy letter if address is current) but the case has educational relevance a waiver of consent is requested (see section 7.5.2).

Some individuals will be over 18 at the age of the consent conversation. If the individual is known to make their own medical decisions, they will be consented. However, if they are not known to make medical decisions, the investigative team will assess if an LAR is in place and request signature from the LAR.

If a non-English speaking study candidate or a legally authorized representative is able to visit an MDBP study site for study enrollment, a certified clinical interpreter will generally be available to facilitate the Short Form consent process, which has been approved for use in this study.

If a certified interpreter is not physically available at the time of the initial MDBP site visit, or if the non-English subject or legally authorized representative is unable to travel to an approved MDBP study site, telephonic interpretation services will be used to facilitate the Short Form consent process. Please refer to Section 7.5.1. for details.

7.5.1 Short Form Consent Process Requiring Telephonic Interpretation Services

The study team will on occasion require the use of an authorized telephonic interpretation service (ex. 'InterpreTalk') to facilitate the Short Form consent process with a non-English speaking study candidate or legally authorized representative. Specifically, telephonic interpretation services will be used in situations where:

a) Neither a qualified in-person interpreter nor the study candidate or legally authorized representative are physically available to meet with a member of the study team for the Short Form consent process;
b) A qualified in-person interpreter is not physically available to meet with a member of the study team, even though the study candidate or legally authorized representative may be.

In either of these cases, an authorized member of the study team will share an approved Short Form consent document in a language native to the candidate or legally authorized representative prior to the consent interview. Upon conclusion of the consent interview, the candidate or legally authorized representative will sign the Short Form consent document and return it to the study team. A member of the study team will then note the name and ID number of the telephonic interpreter in the 'Interpreter/Witness Signature' section of the short form.

7.5.2 Waiver of Consent and HIPAA Authorization

Upon occasion, subjects may become lost to follow-up. This applies in particular to re-consent in patients over the age of 18. A subject will be considered lost to follow up if 3 attempts by phone or email on separate days and separate times and hard copy letter if address is current are unsuccessful in reaching the subject. A waiver of consent and HIPAA authorization (see below) is requested for continued use of the existing data.

There are individual cases where the investigative team has never had contact with the individual and where consent is not possible. In some cases, anonymized data would have great educational relevance, in particular MRI imaging, as a teaching database. In these cases, de-identified records, MRI or CT images will be saved for educational and publication purposes, with no PHI attached. The images or records will be de-identified to remove name, of birth, and location of study and referring physician, such that the records and/or DICOM images with this information will not be able to be retrieved. These images will be stored in a password protected MRI database removed from all other identifying information about the subject. These anonymized data will be linked to the disease state of this individual but not to any PHI. No samples will be kept for these subjects. This approach will only pertain for those patients with whom the investigator has no contact.

Additionally, a waiver of consent will be used for data and samples moved from a similar protocol at Children's National. A waiver of informed consent is requested for these subjects.

The waiver is requested in accordance with 45 CFR 46.116(d):

1) The research involves no more than minimal risk to the subjects;
2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3) The research could not practicably be carried out without the waiver or alteration; and
4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation (though this does not apply to this study)

7.5.3 Waiver of Assent

A request for waiver of assent is requested under 45 CFR 46.408, for those children in whom the capability is so limited that they cannot reasonably be consulted and for subjects for whom a full waiver of consent and HIPAA authorization is being requested. This will be the case of a significant proportion of our patients in whom the severity of the leukodystrophy limits the

ability to provide an assent. For those subjects who are capable of assenting, we will document this in the consent form.

A waiver of assent is also requested for children who are enrolled to the study by phone, as they may not be physically available to participate in the consent interview with the child's parent and/or legal guardian. Children who have the capacity to assent may still do so by signing the appropriate section of the physical consent form mailed to the family following the consent interview.

7.5.4 HIPAA Attestation for the Use of Decedent PHI

This research will utilize the PHI of decedents. In accordance with 45 CFR 164.512(i)(1)(iii), the use or disclosure being sought is solely for research on the protected health information of decedents, the protected health information being sought is necessary for the research, and, at the request of the covered entity, documentation of the death of the individuals about whom information is being sought can be provided.

8 Publication

CHOP staff will have access to complete research files and expect to have significant oversight and involvement in any publication generated from this research.

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APPENDIX A – RELYING SITES

Site Name (FWA No.)	Site Investigator	Investigator Contact Information	Date Added	Reliance Mechanism	Site Responsibilities
University of Wisconsin-Madison (FWA00005399)	Albee Messing VMD, PhD	messing@waisman.wisc.edu	06-06-2017	SMART IRB Agreement	– Recruitment – Data Analysis – Data Collection – Data Management
The Nemours Foundation (FWA00000293)	Grace Hobson, PhD	Grace.Hobson@nemours.org	04-19-2018	SMART IRB Agreement	– Recruitment – Data Analysis – Data Collection – Data Management
Children's Healthcare of Atlanta (FWA00000644)	Stephanie Keller, MD	skelle3@emory.edu	06-04-2019	SMART IRB Agreement (Online)	– Recruitment – Consent – Study Procedures – Data Analysis – Data Collection – Data Management – Regulatory
Emory University (FWA00005792)	Stephanie Keller, MD	skelle3@emory.edu	06-04-2018	SMART IRB Agreement (Online)	– Recruitment – Consent – Study Procedures – Data Analysis – Data Collection – Data Management – Regulatory
Children's National Medical Center (FWA00004487)	Jamie Fraser, MD, PhD	jfraser@childrensnational.org	01-24-2019	SMART IRB Agreement (Online)	– Recruitment – Consent – Study Procedures – Specimen Storage – Data Analysis – Data Collection – Data Management – Regulatory

University of Utah (FWA00003745)	Dr. Joshua L. Bonkowsky, MD, PhD	joshua.bonkowsky@hsc.utah.edu **OR** jbonkowsky@gmail.com	06-14-2019	SMART IRB Agreement (Online)	– Recruitment – Consent – Study Procedures – Data Analysis – Data Collection – Data Management – Regulatory
Kennedy Krieger Institute (FWA00005719)	Dr. S. Ali Fatemi, MD, MBA	fatemi@kennedykrieger.org	06-14-2019	SMART IRB Agreement (Online)	– Recruitment – Consent – Study Procedure – Specimen Storage – Data Analysis – Data Collection – Data Management – Regulatory
The University of Pennsylvania (FWA00004028)	Dr. Jennifer Orthmann-Murphy, MD, PhD	Jennifer.Orthmann-Murphy@pennmedicine.upenn.edu	06-14-2019	PENN-CHOP Master Reliance Agreement (Determination Form)	– Recruitment – Consent – Study Procedures – Data Analysis – Data Collection – Data Management – Regulatory
Massachusetts General Hospital (FWA00003136)	Dr. Florian S. Eichler, MD	feichler@partners.org	TBD	SMART IRB Agreement (Online)	– Recruitment – Consent – Study Procedure – Specimen Storage – Data Analysis – Data Collection – Data Management – Regulatory
Baylor College of Medicine (FWA00000286)	Dr. Lisa T. Emrick, MD	emrick@bcm.edu	TBD	SMART IRB Agreement (Online)	– Recruitment – Consent – Study Procedure – Specimen Storage – Data Analysis – Data Collection – Data Management – Regulatory
Children's Hospital of Colorado (FWA00005070)	Dr. Abigail E. Collins, MD	Abigail.Collins@childrenscolorado.org	TBD	SMART IRB Agreement (Online)	– Recruitment – Consent – Study Procedure – Specimen Storage – Data Analysis – Data Collection – Data Management – Regulatory

Lucile Packard Children's Hospital at Stanford (FWA00000933)	Dr. Keith Van Haren, MD	kpv@stanford.edu	TBD	SMART IRB Agreement (Online)	- Recruitment - Consent - Study Procedure - Specimen Storage - Data Analysis - Data Collection - Data Management - Regulatory

Title:	**New Approaches in Leukodystrophy- the Myelin Disorders Biorepository and Natural History Project**		
Short Title	MDBP		
eIRB Number	14-011236		
Protocol Date:	December 2016		
Amendment 1 Date:		Amendment 4 Date:	
Amendment 2 Date:		Amendment 5 Date:	
Amendment 3 Date:		Amendment 6 Date:	

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Insert and delete terms as relevant

°C	Degrees centigrade
2D gel	Two dimensional gel electrophoresis
AE	Adverse event
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
CLIA	Clinical Laboratory Improvement Amendments
CT	Computed tomography
DNA	Di-ribonucleic acid
eCRF	Electronic clinical research form
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
IPSc	Induced pluripotent stem cells
IRB	Institutional Review Board
GCMS	Gas chromatography mass spectrometry
GUID	Global Unique Identifier
LCMS	Liquid chromatography mass spectrometry
MDBP	Myelin disorders Bioregistry project
MRI	Magnetic Resonance imaging
PCR	Polymerase chain reaction
PHI	Personal health information
PI	Principal investigator
RNA	Ribonucleic acid
RT-PCR	Real time -PCR
SAE	Serious adverse event

ABSTRACT

Context: (Background) Genetic white matter disorders (leukodystrophies) (Vanderver et al., 2015) are estimated to have an incidence of approximately 1:7000 live births. More than a third of these patients never achieve a molecular classification, and many of these disorders lack significant knowledge on molecular mechanisms and natural history. This bioregistry approach proposes to characterize these disorders using available clinical, genetic and molecular approaches to establish novel diagnoses, biomarkers and outcome measures for future clinical diagnostic and therapeutic approaches.

Objectives: (primary and important secondary objectives) The purpose of this study is to: (Aim 1) define novel homogeneous groups of patients with unclassified leukodystrophy and work toward finding the cause of these disorders; (Aim 2) assess the validity and utility of next-generation sequencing in the diagnosis of leukodystrophies; (Aim 3) establish disease mechanisms in selected known leukodystrophies; and (Aim 4) track current care and natural history of these patients to define the longitudinal course and determinants of outcomes in these disorders. This will be achieved by collecting data and samples in a longitudinal fashion across leukodystrophies.

Study Design: The design of this study is observational.

Setting/Participants: The setting of this study will include inpatient and outpatient locations both at CHOP and outside institutions.

The ultimate number of sites is estimated at 10-15. There are currently 2 participating sites.

The number of participants may change over time in this observational study but currently a recruitment ceiling of 12000 cases and their relatives/controls is estimated. All case subjects will be known or suspected to have a leukodystrophy or genetic leukoencephalopathy. Control subjects will be enrolled through non-affected relatives of case subjects.

Inclusion Criteria: Cases

1) Males or females of any age
2) Suspected or confirmed diagnosis of leukodystrophy based primarily on the finding of central nervous system neuroimaging consistent with this diagnosis or on an existing diagnosis of a leukodystrophy or genetic leukoencephalopathy as

defined in existing classification systems (Vanderver et al., 1993, Parikh et al., 2015, Vanderver et al., 2015).

3) Parental/guardian permission (informed consent) and if appropriate, child assent or patient consent

4) Willingness to provide clinical data, participate in standardized assessment and provide biologic samples

Exclusion Criteria: Cases

1) Identification of a diagnosis not consistent with a genetic disorder of the white matter such as an acquired demyelinating condition (e.g. Multiple Sclerosis) or an infectious etiology prior to enrollment, with the exception of sequelae of congenital infections such as CMV
2) Inability to provide consent
3) Weight below safe range for biological sample collection (typically <3kg)

Inclusion criteria: Controls

1) Males or females of any age
2) Individual having a relative with a suspected/confirmed leukodystrophy
3) Parental/guardian permission (informed consent) and if appropriate, child assent or subject consent

Exclusion criteria: Controls

1) Weight below safe range for biological sample collection (typically <3kg)
2) Inability to provide consent

Study Interventions and Measures:

Study procedures include regular and ongoing review and collection of data from of clinical medical records and imaging, biologic sampling for the purpose of research (including blood, skin/tissue biopsy materials, and saliva), biologic samples collected as part of clinical care and for which leftover samples remain after clinical testing (CSF and urine), extra research samples collected at the time of a clinically-indicated procedure, and interviews and questionnaires.

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Genetic white matter disorders (leukodystrophies)(Vanderver et al., 2015) are estimated to have an incidence of approximately 1:7000 live births (Bonkowsky et al., 2010). In the past, patients with white matter disease of unknown cause evaluated by the investigator achieved a diagnosis in fewer than 46% of cases after extensive conventional clinical testing(Vanderver et al., 2012). Even when a diagnosis is achieved, the diagnosis takes an average of eight years(Vanderver et al., 2012) and this "odyssey" results in testing charges to patients and insurers in excess of $8,000 on average per patient, including the patients who never achieve a diagnosis at all(Richards et al., 2015a, Richards et al., 2015b). With next generation approaches such as whole exome sequencing, the diagnostic efficacy is closer to 70%,(Vanderver et al., 2016) but approximately a third of individuals do not achieve a specific etiologic diagnosis. This remaining group of patients (unclassified leukodystrophy) offers the opportunity to describe novel disorders and provide improved diagnostic tools. These diagnostic challenges represent an urgent and unresolved gap in knowledge and disease characterization, as obtaining a definitive diagnosis is of paramount importance for leukodystrophy patients (Kohlschutter and Eichler, 2011).

Moreover, the mechanisms of disease in many leukodystrophies of known cause are very poorly understood: many are systemic abnormalities that manifest only testing white matter. Finally, little is known about the best symptomatic management of the many leukodystrophies without an etiologic cure and thus limited standards of care are available for the management of these patients(Van Haren et al., 2015).

The purpose of this study is to: (Aim 1) define novel homogeneous groups of patients with unclassified leukodystrophy and work toward finding the cause of these disorders; (Aim 2) assess the validity and utility of next-generation sequencing in the diagnosis of leukodystrophies; (Aim 3) establish disease mechanisms in selected known leukodystrophies; and (Aim 4) track current care and natural history of these patients to define the longitudinal course and determinants of outcomes in these disorders.

It is hoped that the present study will help clarify the nosology of the leukodystrophies and significantly advance our understanding of the pathogenesis of these diseases, the best diagnostic testing tools, and the best symptomatic management of these conditions. Due to the breadth of this approach, and the rarity of these conditions, these approaches will be carried out at multiple clinical centers with specialized expertise in the leukodystrophies.

1.2 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

2.1 Aim 1: Define novel homogeneous groups of patients with unclassified leukodystrophy and work toward finding the cause of these disorders

In patients with an unclassified leukodystrophy, the study team will collect as much information as available from existing medical records including existing clinical evaluations, neuropsychological/rehabilitation evaluations, and results from blood, urine, spinal fluid, radiological, and peripheral tissue pathological tests. This data will be evaluated to create nosologic groups amongst patients with unclassified leukodystrophy. Additionally, this aim includes the collection and long-term banking of biological samples in subjects with classified and unclassified leukodystrophies to develop a biorepository. These samples will be compared to samples collected from control subjects, either collected directly from enrolled subjects or through existing banked biological samples .

2.2 Aim 2: assess the validity and utility of next-generation sequencing in the diagnosis of leukodystrophies

In the second aim of this project, unclassified leukodystrophy patients will undergo next generation sequencing approaches including research whole exome, whole genome, RNA sequencing and high throughput genomics analysis in parallel to standard clinical testing to achieve novel molecular classifications. Any genetic findings achieved on a research basis will not be disclosed to participants, but in the context of clinical care may be disclosed if and when they are validated in a CLIA certified setting.

2.3 Aim 3: establish disease mechanisms in selected known leukodystrophies

Specific leukodystrophies will be selected for further mechanistic study, using clinical and laboratory tools to establish increased understanding of the underlying pathophysiology. The over-riding hypothesis of this aim is that integrated biochemical, genomic, metabolic, histologic and immunologic profiles of patients with leukodystrophy will define downstream pathway changes consistent with primary defects causing white matter disease. Appropriate controls will be used for comparison to disease related samples. Samples collected in Aim 1 will be used in these efforts.

2.4 Aim 4: track current care and natural history of these patients to define the longitudinal course and determinants of outcomes in these disorders.

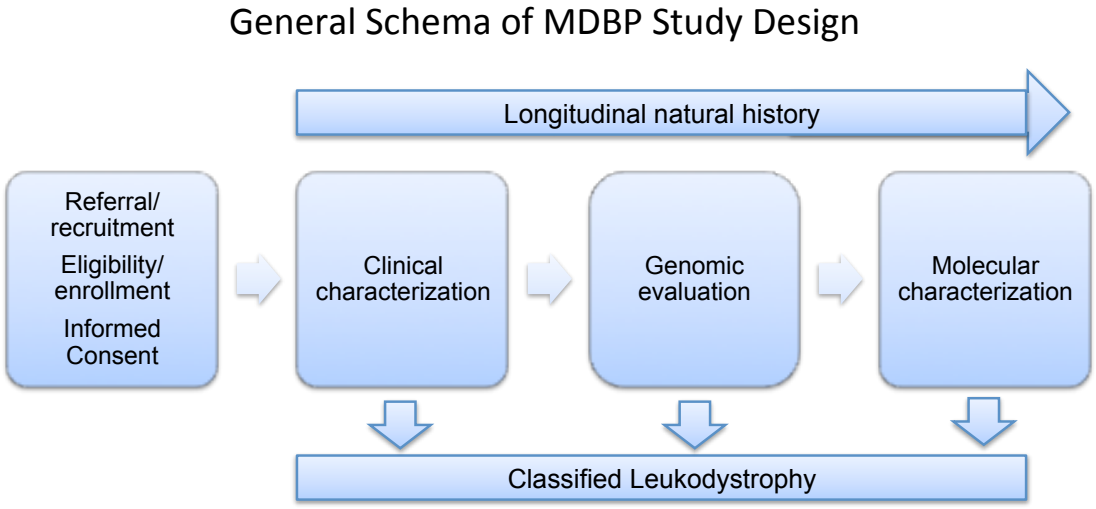
The final aim includes maintaining a longitudinal collection of clinical data on disease presentation, progression, morbidities and the therapeutic interventions in leukodystrophy patients and related controls.

Table 1. Delineation of clinical versus research Interventions used to obtain data for MDBP

Aim	Data collected from standard of care clinical approaches	Data collected explicitly for research purposes
1	Medical records depicting neurologic examinations, laboratory findings, and other clinical care delivered to the patient Copies of MRIs or other imaging performed as part of clinical care Leftover samples (blood, urine, biopsy tissue, CSF and others) collected during procedures done for medical care	Research only samples including: -Blood for collection of genomic DNA -skin punch (3-4mm) biopsy for the purpose of establishing iPSc or cells for functional analysis, excluding those subjects <1 year of age and at greater risk of scarring -Leftover samples from clinical care including blood, urine, biopsy tissues, CSF and others, collected at the time of procedures done for medical care -Extra samples (blood, urine, and CSF only) collected at the time of procedures done for medical care
2	Existing genomic data performed as part of clinical sequencing, and collected for re-analysis	Generation of research WES, WGS, RNA seq or other sequencing approaches
3	None	Samples banked in 1 will be submitted to analyses including histologic, immunologic, genomic, metabolomic, proteomic, and biochemical approaches for the purpose of identifying changes that may help determine the molecular etiology or downstream changes related to the mechanism of disease
4	Medical records depicting clinical care delivered to the patient including records of hospitalizations and interventions Copies of MRIs or other imaging performed as part of clinical care	Functional outcome measures Patient reported outcome measures including quality of life surveys

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design (Figure 1)



The following five phases of participation are reviewed: Referral/enrollment, clinical characterization, genomic evaluation, molecular characterization, and longitudinal natural history. Case subjects may be included, depending on the characteristics of their individual disorder and research interest in all or only some parts of this general schematic.

3.2 Study Duration, Enrollment and Number of Sites

Given the need for robust longitudinal data on leukodystrophy subjects and controls, there is no specific timeframe for this study. Data collection may continue for the foreseeable future. Ongoing data collection for leukodystrophy subjects will continue as frequently as possible dependent on the clinical care schedule. Comparative control data may also be collected if possible, to enable the ongoing comparison of outcomes to cases.

The number of participants may change over time in this observational study but currently a recruitment ceiling of 12000 cases and their relatives/controls is estimated. All case subjects will be known or suspected to have a leukodystrophy or genetic leukoencephalopathy. Control subjects will be enrolled through non-affected relatives of case subjects.

The ultimate number of sites is estimated at 10-15. There are currently 2 participating sites.

3.2.1 Duration of Study Participation

There is no strict schedule of visits for any subjects. For cases, new data collection is expected approximately every 6 months, consistent with the typical minimal interval at which a leukodystrophy patient is seen clinically. Additional data will be collected when the subject has an event complicating the leukodystrophy, such as an unexpected hospitalization (such as for an aspiration pneumonia), or an anticipated event (such as an elective surgery for a gastrostomy tube placement). Duration of the study for an individual case subject will vary depending on a specific subject's clinical care needs and whether or not s/he is being seen regularly at a

participating study site. Data and samples may continue to be collected on control subjects for the purpose of ongoing comparisons between cases and controls.
Samples will be retained indefinitely, to assist in the identification of rare entities, which may present only in an exceptionally small number of individuals, and to assist in the development of biomarkers for established disorders.

3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

There are currently two enrolling sites: CHOP and Children's National Medical Center. Additional sites may be added with future protocol revisions. Due to the relative rarity of these conditions, it is expected that at least 10-15 clinical sites will be included in this bioregistry.

3.3 Study Population

3.3.1 Inclusion Criteria: Cases

1) Males or females of any age
2) Suspected or confirmed diagnosis of leukodystrophy based primarily on the finding of central nervous system neuroimaging consistent with this diagnosis or on an existing diagnosis of a leukodystrophy or genetic leukoencephalopathy as defined in existing classification systems (Vanderver et al., 1993, Parikh et al., 2015, Vanderver et al., 2015).
3) Parental/guardian permission (informed consent) and if appropriate, child assent or patient consent
4) Willingness to provide clinical data, participate in standardized assessment and provide biologic samples

3.3.2 Exclusion Criteria: Cases

1) Identification of a diagnosis not consistent with a genetic disorder of the white matter such as an acquired demyelinating condition (e.g. Multiple Sclerosis) or an infectious etiology prior to enrollment, with the exception of sequelae of congenital infections such as CMV
2) Inability to provide consent
3) Weight below safe range for biological sample collection (typically <3kg)

3.3.3 Inclusion criteria: Controls

1) Males or females of any age
2) Individual having a relative with a suspected/confirmed leukodystrophy
3) Parental/guardian permission (informed consent) and if appropriate, child assent or subject consent

3.3.4 Exclusion criteria: Controls

1) Weight below safe range for biological sample collection (typically <3kg)
2) Inability to provide consent

3.4 Study Procedures

3.4.1 Screening and enrollment

Case subjects will be identified through various mechanisms. Initial identification will most commonly occur through the subject's clinical leukodystrophy specialist or neurologist, but the study team may also be contacted directly by a subject or the subject's caretaker and contact information/indication of interest in the study will be provided by the family via a secure database, REDcap. The study will be discussed with the prospective subject's parents and consent will be obtained. Subjects will be informed during the consent process that their medical information, including MRI imaging, will be reviewed to confirm the case subject meets the required inclusion/exclusion criteria. If a finding is made in this period that suggests that subject does not have a leukodystrophy, the family will be informed and their participation will be ended. For all other subjects, once the initial screening period is completed, subjects will continue directly into the Observation period.

Subjects may be seen in person but may also participate remotely by forwarding their biological samples and data to the researchers for inclusion in the database and biorepository once informed consent has been obtained.

Control subjects will be identified through enrolled case subjects and will be approached for consent either in person or on the phone. Control subjects will be enrolling directly into the observational period; there are no required screening procedures though there is a possibility that the subject would be removed from the study if an underlying medical condition is discovered that would complicate comparative analyses.

3.4.2 Observational Period (initial visit and follow up visits)

Due to the rarity and complexity of leukodystrophies, the clinical assessment and diagnosis of these patients can be complicated and may involve testing and expertise across multiple medical specialties. This leads to a "standard of care" that is variable across providers and institutions. This can be problematic for all leukodystrophy patients, particularly those with unclassified leukodystrophies. For this reason, this study will implement a standard process for collecting medical record data from commonly shared variables and test findings to better identify common themes and trends in the treatment of these patients. Subjects will be asked provide biologic samples as described in section 4.2. Patients will also undergo standardized assessments as provided in section 4.3.

3.4.2.1 *Clinical Characterization:*

Detailed clinical information will be collected for enrolled leukodystrophy subjects and analyzed in a standardized, descriptive fashion to identify novel nosologic groups to identify novel disorders within the classified leukodystrophies. Medical records with relevance to understanding the proband's genetic and medical background, including prenatal records if the mother is consented

as a control subject, will be reviewed and abstracted. Subjects will provide consent for the study, which will include review of their medical records and then, of these medical records come from outside of CHOP, will need to also sign a release of medical information form. Previous and ongoing evaluations including standard biochemical, genetic, neurophysiologic and neuroimaging studies will be reviewed.

Biological samples will also be collected from leuokodystrophy subjects for analyses and long-term storage in a biorepository. The study team will make every effort to collect research samples at the time of clinically indicated testing. These samples will include urine, blood, tissue, fibroblasts or cerebrospinal fluid. If tissues are obtained for clinical diagnostic purposes (biopsies of brain, liver, muscle for example), leftover sample not used for pathologic analyses may be banked. In cases where clinically indicated venipuncture is not occurring, blood samples may be obtained for research purposes. In some cases, the investigator may request extra research samples (blood, urine, CSF) to be collected at the time of a clinically-indicated procedure, provided that the total (research + clinical) sample amount/volume does not exceed a clinically accepted definition of “minimal risk.” Saliva may be obtained for research purposes. In cases where this tissue is not available a skin punch biopsy (3-4mm) may be performed. Punch biopsies for research purposes will not be performed in individuals under a year of age or at greater risk of scarring.

Control data/samples will be collected both from the medical records, interviews, and questionnaires from healthy family members of leukodystrophy patients and from pre-existing tissue banks (fibroblast cultures, cerebrospinal fluid).

3.4.2.2 *Genomic evaluation:*

Research genetic testing, including whole exome, whole genome, RNA sequencing and high throughput genomics analysis testing will be done in leukodystrophy and control samples through the collection of biological samples, both specifically for research purposes and leftover samples remaining after clinical care procedures. Genetic findings from research testing will not be returned to families. Novel genes will not be disclosed to families until a peer-reviewed manuscript is accepted for publication and confirmatory testing has occurred in a CLIA certified laboratory. Genetic testing results will not be returned to families as part of this research, but will be returned in a clinical setting after CLIA certified testing has occurred.

3.4.2.3 *Molecular characterization:*

Case subjects with specific leukodystrophies will be selected for further mechanistic study, using clinical and laboratory tools to establish increased understanding of the underlying pathophysiology. In this select group, biological samples will be submitted to analyses including histologic, immunologic, genomic, metabolomic, proteomic, and biochemical approaches for the purpose of identifying changes that may help determine the molecular etiology or downstream changes related to the mechanism of disease.

3.4.2.4 ***Natural history:***

For most leukodystrophies, the natural disease course including age at presentation, features of disease, long term complications and standard symptomatic management and their impact are unknown. This aim will review and record case subject reported outcomes as well as clinical records to create a longitudinal dataset of these features. Established functional outcome assessments (which may include as an example the Gross Motor Function Measure 88, neurocognitive function and other established tools) may be used in selected leukodystrophies. Finally, patient reported outcomes would be generated from case and control subjects in standardized intervals, which may include quality of life questionnaires to help characterize the impact a diagnosis of leukodystrophy has on a patient and family.

A unique identifier linking the family member and their relationship to the case will be created in the study database.

De-identified control samples will also be obtained from several sources (see section 4.2).

3.5 Subject Completion/Withdrawal

Withdrawal from the study is permitted at any time and would result in removal of any identifying information from recorded databases and destruction of any biological samples collected. Withdrawal from the study will also suspend any further medical record data collection.

Samples that have been deidentified in the course of research applications will remain in the repository as it would not be possible to identify the sample for removal. Additionally, deidentified samples that have been sent to collaborators may not be able to be retrieved.

4 STUDY EVALUATIONS AND MEASUREMENTS

4.1 Medical Record Review

Elements of history and examination pertinent to the diagnosis of a leukodystrophy for case subjects will be recorded in a database. Available neuroimaging, neurophysiologic, biochemical and molecular data for individual case subjects will be reviewed and recorded (see appendices and data collection forms). Records will be requested for any biochemical and molecular studies performed as part of clinical care for case subjects and family member subjects, if relevant for comparison to the relative's case data. Data from previously performed next generation sequencing approaches will be requested for review for all subjects.

Minimal medical history information will also be collected upon occasion from family members and will be primarily targeted at elucidating better understanding of the cases' condition, based on information in their relative's medical history.

4.2 Collection of Biological Samples

Biological samples will be collected from leuokodystrophy subjects and related controls/family members for analyses and long-term storage in a biorepository. If the subjects are seen at the study site, the blood will be collected following local SOPs for collection of research specimens

and will be done at the same time as a clinical sample collection, if possible. If the subjects are not seen at the study site, they will be instructed to have blood collected at their local physician's office or another collection center (i.e. Quest) and the sample forwarded for storage in the biorepository.

Samples will be assayed according to techniques selected among standard laboratory manipulations, including histologic, immunologic, biochemical, genomic and proteomic techniques including the following: immunohistochemistry, histochemistry, cell culture and cellular based experiments, live cell imaging, ELISA, multiplex measurements of cytokines, chemokines, and antibody arrays, GC and LCMS small molecule measurement, Gene expression profiling, RT PCR, standard sequencing, next generation sequencing, western blot, 2D gel analysis, low molecular weight proteomics, shot gun proteomics.

4.2.1 Peripheral blood collection

A blood sample or filter paper blood sample may be obtained for studies of genomic DNA, RNA or disease specific analytes in cases and control subjects. Additionally, serum and plasma may be banked for culture. Peripheral blood cells may be transformed as lymphoblastoid cell lines or iPSc generation. The blood draws will not exceed the NIH limits of no more than 5 ml/kg in a single day, and no more than 9.5 ml/kg over an 8-week period. Blood sampling is not expected for patients under 3kg.

4.2.2 CSF sample collection

Leftover cerebrospinal fluid samples will be collected in leukodystrophy subjects after clinically-mandated lumbar puncture. The investigator may request extra CSF to be collected at the time of a clinically-mandated lumbar puncture, provided that the total (research + clinical) volume of CSF collected falls within the clinical guidelines for CSF collection (see below). Any available leftover cerebrospinal fluid will be banked.

Collection of CSF samples should not exceed reasonable estimations of CSF production and replacement**. Evidence suggests as well as in** that in **children and adults** (defined in these studies as 9 years to 61 years **in source documentation**)**, CSF production is greater than 0.3ml/min or 0.02-0.05% of the total volume per minute, with a turn-over of the entire brain CSF in adults approximately 3-5 times per day. In children and adults, total CSF volume is estimated at 150 cc. Total CSF volume in a newborn is estimated to be 50 ml and to increase gradually with age to an adult volume. Thus, in an infant, CSF production is estimated at about 6-10 cc per hour and in older children about 18 cc per hour. In this investigator's previous experience on other protocols, in children 10 years and above, 15cc of CSF is commonly collected knowing that this volume will be repleted in one hour. In infants and younger children more moderate volumes are typically recommended, and the investigator has used 5 cc in infants and 10 cc in children. There are no published norms for this that the investigator is aware of but the investigator proposes:**

Age of subject	Total amount of sample drawn (**including any clinical labs that need to be obtained during**

	the same lumbar puncture)
Neonate at least 3kg to <4 years and 15kg	5cc, no more than once in a one week period
4 years and 15 kg to 10 years and 30 kg	10 cc, no more than once in a one week period
≥10 years and 30kg	15 cc, no more than once in a one week period

CSF will not be collected from family members

4.2.3 Saliva collection

A saliva sample may be collected from cases and related controls/family members for the specific purpose of DNA/RNA extraction.

4.2.4 Skin punch biospy

In select circumstances, additional procedures may be performed in cases such as a skin punch (3-4mm) biopsy that will not require anesthesia/sedation or sutures. Fibroblasts may be collected for the express purpose of obtaining patient cells for analysis of identified candidate genes/function and or the creation of cell lines including iPS (induced pluripotent stem) cells. If a clinically indicated skin biopsy has been performed, and banked cells exist, those specimens will be sought and obtained rather than impose a repeat skin biopsy. Punch biopsies on a research basis will not be performed in those individual under a year of age or at greater risk of scarring.

These samples will not be collected from related controls/family members.

4.2.5 Urine collection

Urine from case subjects will be processed from leftover clinical sample collected for clinically indicated reasons, if available. The investigator may also request extra urine to be collected for research purposes at the time of a clinical visit or inpatient stay, provided that this falls within the clinically accepted guidelines for urine sample collection.

4.2.6 Additional Tissue Samples

If cases have additional clinical testing during which other tissue samples are obtained (for example a nerve, muscle, liver or brain biopsy), leftover biopsy material after clinically indicated pathologic studies are completed may be banked. We may also ask to collect previously banked filter paper blood spots (such as newborn screening samples).

4.2.7 Additional Control Samples

In addition to the samples collected above, additional control data/samples may be obtained from pre-existing tissue banks (fibroblast cultures, cerebrospinal fluid). The investigators will not be able to readily ascertain the source of these samples (e.g. de-identified, or coded samples from a collaborator [the code will not be provided]). These are outlined in the table below. If the data/samples are being provided by a data registry, biospecimen repository or other data source, the investigators will maintain documentation that either of the following is in place: (1) policies and procedures that prevent the release of identifiers; or (2) an agreement in place between the data source and the investigator stating that no identifiers will be released under any circumstances. Research on samples/data which are not readily identifiable does not constitute human subjects research. Therefore, the individuals whose not readily identifiable data/samples are included in this research will not be included in the enrollment numbers for this study and research activities using these samples/data will not be reported as part of the continuing review.

Table 3. Examples of control subjects
In the case of blood or saliva samples (consent will be sought)
Healthy family volunteers
In the case of cerebrospinal fluid (pre-existing specimens, consent will not be sought)
Pre-existing banks of cerebrospinal fluid of patients with traumatic brain injury, brain tumor, aseptic meningitis or other neurologic disorders (anonymous samples).
In the case of fibroblasts (pre-existing specimens, consent will not be sought)
Banked anonymous fibroblast cell cultures of healthy control subjects

4.3 Questionnaires/Interviews/Standardized assessments

All subjects may be asked at varying times over the course of the study to complete questionnaires to help characterize the impact a diagnosis of leukodystrophy has on a patient and family and to help establish the natural history of leukodystrophies. Additionally, case subjects may undergo standardized testing assessments to establish functional outcomes. Lists of commercially-available outcome measures used in the study are provided in the attachments to the IRB application and include established functional outcome assessments (which may include as an example the Gross Motor Function Measure 88 and other established tools). Finally, patient reported outcomes will be generated on standardized intervals, which may include quality of life questionnaires to help characterize the impact a diagnosis of leukodystrophy has on a patient and family.

5 STATISTICAL CONSIDERATIONS

5.1 Statistical Methods

The bulk of data to be collected will be descriptive in nature. In order to characterize the clinical features of the different types of leukodystrophies, we will compare the various classified and unclassified leukodystrophies based on either analysis of variance or covariance for

measurement outcomes or contingency table analysis or logistic regression for categorical variables. T- of F-statistics will be used to identify statistically significant differences in the means between groups and chi square values will be used to identify statistically significant differences in the frequency of categories between groups. This analysis will help us identify those factors that are common to many or all forms of leukodystrophies and those that may be unique to the unclassified forms. We will pay particular attention in subsequent analyses to those features that are distinctive among the groups. Subsequent analyses will employ two distinct methods of data reduction, one statistical, exploratory factor analysis, and one heuristic, neural network analysis, to attempt to define subtypes based on clinical features within the unclassified group. By comparing the results of the two methods, we will be able to identify those subtypes for which there are not agreement between the different methods.

5.1.1 Sample Size and Power

The data reduction/classification steps are viewed as hypothesis generating and thus have not subjected to power analysis.

5.2 Control of Bias and Confounding

The subjects in this observational study will not assigned by a process of randomization and are therefore subject to bias. The descriptive approach to analyses and the hypothesis generating approaches will be less likely than other approaches to be significantly affected by these confounders. There is no possibility for randomization or controlled experimentation in these approaches.

6 SAFETY MANAGEMENT

6.1 Safety Evaluation

There is no formal Data Safety Monitoring Board for this study. Subjects will be continuously monitored for adverse events, excluding those anticipated in leukodystrophy patients, such as respiratory, gastrointestinal, and bone complications of these disorders (Van Haren et al., 2015). Adverse events related to study related procedures, in particular to research only procedures, would be documented and reported as detailed below. If unexpected adverse events occur, the investigator will meet with the IRB and determine if a more robust data safety plan would be beneficial to provide additional oversight over study activities.

6.2 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study. These are not anticipated in relation to the study procedures, though we expect unrelated adverse events including death to occur in these individuals due to the natural history of these disorders (Van Haren et al., 2015).

6.3 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review. Anticipated adverse events unrelated to study procedures, related to the severe natural history of these conditions (Van Haren et al., 2015), will not be reported.

7 STUDY ADMINISTRATION

7.1 Data Collection and Management

The study data will be retained in the study-specific REDcap data base at CHOP and the NeuroBANK™ database. NeuroBANK™ is a collaboration and data repository platform maintained by the Massachusetts General Hospital (MGH) Neurological Clinical Research Institute (NCRI). This platform facilitates:

1. Capture of clinical and research data from neurologic patients for individual projects in a structured and secure system;
2. Aggregating and sharing uniform, de-identified and/or anonymized datasets for secondary analyses.

Data management (DM) at NeuroBANK™ is responsible for the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with applicable sponsor and regulatory requirements. Site personnel will collect, transcribe, correct, and transmit the data onto source documents, case report forms (CRFs), and/or other forms used to report, track and record clinical research data. DM is responsible for developing, testing, and managing clinical data management activities. The NeuroBANK™ platform provides password protection. An edit checking and data clarification process will be put in place to ensure accuracy of the data. Logic and range checks as well as more sophisticated rules may be built into the eCRFs to provide immediate error checking of the data entered. The system has the capability to automatically create electronic queries for forms that contain data that are out of range, out of window, missing or not calculated correctly. The sites will only have access to the queries concerning their subjects. Identifying information about subjects will only be visible to site specific personnel. CHOP and NeuroBank personnel would additionally have access to non-identifying data for validation and monitoring of data.

For samples from healthy family members, a unique identifier linking the family member and their relationship to the proband will be created.

7.1.1 Sample Retention

All samples will be stored in dedicated freezer space using coded freezer safe label systems with barcode identification. Those samples (such as filter paper blood spots or paraffin embedded blocks or slides) able to be banked in non-refrigerated settings will be kept in a locked cabinet.

Coded samples may be shared with researchers in the U.S. or other countries to perform additional research, place it into research databases, or use it to improve the design of future studies. These samples will be de-identified to the recipients but site investigators will retain a mechanism to identify the subject. If clinically relevant information is found or further information with regards to a sample is wanted by the outside researcher/institution, only approved study personnel will contact the participant. Coded fibroblast samples will be sent to collaborators, for establishment and research of human induced pluripotent stem (iPS) cells. At no point will the outside researcher/institution have access to PHI of the participants.

7.1.2 Data sources

Data sources will include clinical notes, neuroimaging reports, laboratory evaluations and other clinical evaluations, both at CHOP and outside institutions. Original radiology studies and genomic data sets may also be used. Bioregistry samples will be used. Previously collected data and samples from Children's National Health System will be used in this bioregistry. Additionally, existing banks of de-identified samples may be used.

7.2 Confidentiality

All data and records generated with this study will be kept confidential in accordance with institutional policies and HIPAA requirements (as applicable). The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. For data stored in the NeuroBANK™, a Global Unique Identified (GUID) number will be used as an identifier for that subject. The GUID is an 11 Character string that is generated using an encryption technology and algorithms licensed by the NCRI from the National Institutes of Health (NIH). The GUID is generated on a secure website that utilized 128-bit Secure Socket Layer (SSL). Of note, this website is not directly linked to GLIA or NeuroBANK. The GUID is generated using an irreversible encryption algorithm – it accepts twelve identifying elements (e.g. Last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth etc), and produces a unique random generated character or string, the GUID. No identifying system is stored in the system; it is simply used to generate the GUID. If the same information is entered again at another site for example, the same GUID is returned. Identifiers will only be linked to patient names through a password-protected database, accessible only to site study personnel.

Names are maintained in a site-specific database available only to members of the study team in order to provide patients with clinically relevant information generated from this study. No identifiable data will be used for future study without first obtaining IRB approval. Any data or samples shared outside of CHOP will be done so in a coded fashion with no PHI included and with the execution of all applicable agreements (i.e. MTA). In rare circumstances, if PHI must accompany the data/sample, only the minimal necessary PHI will be included and, again, in

accordance with the provisions of all applicable agreements executed for the transfer (i.e. DUA). The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at CHOP) before sharing a limited dataset (dates and zip codes).

7.3 Regulatory and Ethical Considerations

7.3.1 Data and Safety Monitoring Plan

Procedures of this study are minimal risk and primarily related to the collection of biological samples and confidential information. The Principal Investigator and associate investigators will monitor adverse events, including collection of biologic samples and identification of genetic testing results and report these as detailed above to the IRB. If unanticipated adverse events are noted that change the risk assessment of the study or informed consent, modifications to the study protocol and informed consent documents will be discussed with and submitted to the IRB. Adverse events related to study related procedures, in particular to research only procedures, would be documented and reported as detailed above. If unexpected adverse events occur, the investigator will meet with the IRB and determine if it would be beneficial to provide additional oversight over study activities.

7.3.2 Risk Assessment

The risks of this study are minimal and primarily related to the collection of biological samples and confidential information. Physical risks may result from the collection of blood samples specifically for the research and skin punch biopsy. Punch skin biopsies for research only will not be performed in subjects under a year of age and at greater risk of scarring.

Risks have been minimized as much as possible. Many samples will be leftover samples available after clinically indicated procedures or will be collected in tandem with clinically-performed procedures. In some cases, the investigator may request extra research samples to be collected at the time of a clinically-indicated procedure, provided that the total (research + clinical) sample amount/volume does not exceed a clinically accepted definition of “minimal risk.” Results from genetic testing will not be returned to families, though the study will collect the findings of any genetic testing done as part of the subjects’ clinical care.

As all subjects participating in this study have already received a diagnosis of leukodystrophy there is little risk of discrimination (legal or social) based on participation in this study. Finally, there is the risk of psychosocial stress by being asked to fill out patient reported outcome and quality of life surveys.

7.3.3 Potential Benefits of Study Participation

There is no intended direct benefit of participation. There is a potential for indirect benefit in developing better diagnosis, further understanding of pathogenesis and outcome markers for clinical trials. We believe that this study will result in new pathophysiologic understanding of these complex disorders, new biomarkers for difficult to diagnose entities and documentation of novel disorders. In addition, as the project evolves and clinically relevant biomarkers for specific

disorders are established, validated, and published, clinically relevant results will be reported to the treating physician.

Over the history of this bioregistry protocol, previously at Children's National Medical Center, data collected has led to the identification of several new disorders(Rice et al., 2009, Bernard et al., 2010, Bernard et al., 2011, Tetreault et al., 2011, Rice et al., 2012, Steenweg et al., 2012, Depienne et al., 2013, Kevelam et al., 2013, Simons et al., 2013, Taft et al., 2013, Dallabona et al., 2014, Pizzino et al., 2014, Rice et al., 2014, Simons et al., 2015, Thiffault et al., 2015, Dallabona et al., 2016, Jenkinson et al., 2016), biomarkers of disease in a number of leukodystrophies (Vanderver et al., 2005, Steenweg et al., 2010, Prust et al., 2011, Brown et al., 2012, Rice et al., 2013, Han et al., 2014, Vanderver et al., 2014, Cuadrado et al., 2015, Jany et al., 2015, La Piana et al., 2016), and two clinical trials, currently ongoing, in Aicardi Goutieres Syndrome(Crow et al., 2014). Thus, we feel that although there is no intended direct benefit, there is potential for significant indirect benefit.

7.3.4 Risk-Benefit Assessment

Though there is no direct benefit to participating, it is expected that this research study will permit better understanding of leukodystrophies, which in time, is expected to result in new treatment options. Given nature of the procedures involved in participating, we feel the risk to benefit assessment is appropriate.

7.4 Recruitment and referrals

Leukodystrophy patients will be identified through various mechanisms. Initial identification will most commonly occur through the subject's clinical leukodystrophy specialist or neurologist, but specific recruitment and referrals approaches may occur and are detailed below.

7.4.1 Referrals

Patients with leukodystrophies will be referred from within a participating institution, including CHOP, or from outside collaborating institutions for inclusion in the study. Outside physicians who believe their patients are eligible will be asked to provide patients with contact information for the PI/co-PIs/Co-Investigators/study coordinator. If interested, prospective participants will contact the PI/co-PIs/Co-Investigators/study coordinator and asked to complete a survey to collect contact information and research or clinical interests. Once complete, the potential participant will be contacted by a qualified study staff member to review these interests and conduct the informed consent conversation if indicated.

Because of the nature of leukodystrophy, the community is very active in seeking any opportunities to learn more about their condition. As such, there will also be occasions when the study team is contacted directly by a subject or the subject's current clinical care provider. Additional referrals may come from word of mouth or patient advocacy groups.
Subjects may be seen in person but may also participate remotely by forwarding their biological samples and data to the researchers for inclusion in the database and biorepository. Additionally,

online password protected databases, such as Redcap will be used to collect referral information prior to inclusion of consented patients in NeuroBANK.

7.4.2 Recruitment Strategy

Additional recruitment approaches may be used. Outside physicians who have submitted samples to the PI for previous studies of leukodystrophy will be contacted to inform them of the study. Lab directors whose labs perform genetic testing for select genes related to leukodystrophy will be asked to provide information about this research to referring physicians (see recruitment materials). Additional procedures for recruitment may include the Myelin Disorders Bioregistry websites (www.myelindisorders.org, www.theglia.org) or database generated surveys to referral families such as Redcap Survey® or Patient Reported tools such as those included in NeuroBANK™. In addition, study information (title of study, PI, contact information) will be posted on appropriate websites such as www.clinicaltrials.gov.

7.5 Informed Consent/Assent and HIPAA Authorization

Informed consent will be mailed/ or emailed to prospective participants and reviewed over the phone prior to signing for participants not coming to a study site for clinical evaluation and will be completed in person by all participants coming to a study site for clinical evaluation. Patients who wish to enroll from outside a study site will be sent a separate instruction sheet for how to enroll, send samples, and how to arrange a clinic visit as appropriate. When possible every effort will be made for this clinical evaluation to include a neurologic exam by the PI or qualified co-investigators in addition to a comprehensive chart review. When it is not possible for the PI/co-PI/Co-investigator to conduct a neurologic exam, records of previous neurologic exams will be requested in addition to other medical records.

For subjects enrolled at the institution where they receive care, subjects will be informed that their decision to participate will in no way impact the care that they receive or the access they currently have to their provider. The study will be discussed in a private room or on the telephone with sufficient time allotted for the subject to ask questions and decide whether they want to participate. The study team will make every attempt to ensure subjects understand that they are under no obligation to participate. The majority of the procedures being proposed would be done as part of the subject's clinical care, regardless of whether they choose to enroll. The study team will emphasize that the subject does not need to participate to proceed with the testing their clinician recommends. If desired, subjects will be permitted to take a copy of the consent form home for review.

Since leukodystrophies primarily affect children, many participants will be under the age of 18 at time of study enrollment. If further research is being done and the participant is noted to be near or at the age of 18, the study team will attempt to reach out to obtain re-consent from the participant. If the participant is legally incapacitated, re-consent will be obtained from a legally authorized representative (LAR). The study team will specifically discuss with the LAR their role as the patients representative to assess this relationship. If efforts to reach the participant are not successful (3 attempts by phone or email on separate days and separate times and hard copy

letter if address is current) but the case has educational relevance a waiver of consent is requested (see section 7.5.2).

Some individuals will be over 18 at the age of the consent conversation. If the individual is known to make their own medical decisions, they will be consented. However, if they are not known to make medical decisions, the investigative team will assess if an LAR is in place and request signature from the LAR.

When the patient, relatives or LAR are non English speaking, a certified clinical interpreter will be used, in person or by phone, for the consent conversation. In cases where interpretation is required for the consent conversation, including when the conversation is occurring offsite and by phone, the presence, time and name of the interpreter will be documented on the consent form. If the consent is occurring in person, on site, the interpreter will be asked to sign to document their presence during the consent conversation.

7.5.1 Waiver of Consent and HIPAA Authorization

Upon occasion, subjects may become lost to follow-up. This applies in particular to re-consent in patients over the age of 18. A subject will be considered lost to follow up if 3 attempts by phone or email on separate days and separate times and hard copy letter if address is current are unsuccessful in reaching the subject. A waiver of consent and HIPAA authorization (see below) is requested for continued use of the existing data.

There are individual cases where the investigative team has never had contact with the individual and where consent is not possible. In some cases, anonymized data would have great educational relevance, in particular MRI imaging, as a teaching database. In these cases, In these cases, de-identified records, MRI or CT images will be saved for educational and publication purposes, with no PHI attached. The images or records will be de-identified to remove name, date of birth, date and location of study and referring physician, such that the records and/or DICOM images with this information will not be able to be retrieved. These images will be stored in a password protected MRI database removed from all other identifying information about the subject. These anonymized data will be linked to the disease state of this individual but not to any PHI. No samples will be kept for these subjects. This approach will only pertain for those patients with whom the investigator has no contact.

Additionally, a waiver of consent will be used for data and samples moved from a similar protocol at Children's National. A waiver of informed consent is requested for these subjects.

The waiver is requested in accordance with 45 CFR 46.116(d):

(1) the research involves no more than minimal risk to the subjects;

(2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) the research could not practicably be carried out without the waiver or alteration; and

(4) whenever appropriate, the subjects will be provided with additional pertinent information after participation (though this does not apply to this study)

7.5.2 Waiver of Assent

A request for waiver of assent is requested under 45 CFR 46.408, for those children in whom the capability is so limited that they cannot reasonably be consulted and for subjects for whom a full waiver of consent and HIPAA authorization is being requested. This will be the case of a significant proportion of our patients in whom the severity of the leukodystrophy limits the ability to provide an assent. For those subjects who are capable of assenting, we will document this in the consent form.

A waiver of assent is also requested for the children who are enrolled to the study under a waiver of documentation of consent/HIPAA Authorization as they may not be available at the time the study is discussed to join the call.

7.5.3 HIPAA attestation for the use of decedent PHI

This research will utilize the PHI of decedents. In accordance with 45 CFR 164.512(i)(1)(iii), the use or disclosure being sought is solely for research on the protected health information of decedents, the protected health information being sought is necessary for the research, and, at the request of the covered entity, documentation of the death of the individuals about whom information is being sought can be provided.

8 PUBLICATION

CHOP staff will have access to complete research files and expect to have significant oversight and involvement in any publication generated from this research.

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APPENDIX

No appendices are included

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RESEARCH PROTOCOL

TITLE: New Diagnostic and Therapeutic Approaches in Leukodystrophy

RESEARCH PLAN

A. Specific Aims

1. Precis:

Genetic white matter disorders (leukodystrophies) are estimated to have an incidence of approximately 1:7000 live births[1]. As many as 50% of patients with white matter disease remain undiagnosed after conventional neuroimaging, biochemical and genetic testing, and therefore have unsolved leukodystrophies. Moreover, the mechanisms of disease in many leukodystrophies of known cause are very poorly understood: many are systemic abnormalities that manifest only testing white matter. Finally, little is known about the best symptomatic management of the many leukodystrophies without an etiologic cure and thus no standards of care are available for the management of these patients. The purpose of this study is to: (a) define novel homogeneous groups of patients with leukodystrophy and work toward finding the cause of these disorders; (b) establish disease mechanisms in selected known leukodystrophies; (c) track current care and natural history of these patients to define the longitudinal course and determinants of outcomes in these disorders; and (d) assess the clinical validity and utility of next-generation sequencing in the leukodystrophies. In order to achieve these goals, patients with leukodystrophy will be analyzed by clinical, neurophysiological, biochemical and genetic means. For goal (a), patients would have been diagnosed as having an unsolved leukodystrophy or no known cause of their leukodystrophy at outside centers. In such patients, the PI and co-investigators will review existing clinical evaluations, neuropsychological/rehabilitation evaluations, blood, urine, spinal fluid, radiological, and peripheral tissue pathological tests. Where feasible, a known leukodystrophy will be identified in these patients. Banked specimens will be collected for these patients for future analysis. For goal (b), selected leukodystrophies with a defined genetic cause will be selected for further mechanistic study, using clinical and laboratory tools to establish increased understanding of the underlying pathophysiology. For goal (c) detailed clinical data including medical complications, hospitalizations, standardized functional assessments, patient reported outcomes and laboratory and radiologic testing will be reviewed and recorded. For goal (d) leukodystrophy patients will undergo Whole Genome Sequencing (WGS) in parallel to standard clinical testing in a staggered fashion. It is hoped that the present study will help clarify the nosology of the leukodystrophies and significantly advance our understanding of the pathogenesis of these diseases, the best diagnostic testing tools, and the best symptomatic management of these conditions. Due to the breadth of this approach, and the rarity of these conditions, these approaches will be carried out at multiple clinical centers with specialized expertise in the leukodystrophies.

2. Objectives and specific aims.

The broad objectives of the present protocol are: (a) define novel homogeneous groups of patients with leukodystrophies and work toward finding the cause of these disorders; (b) establish

disease mechanisms in selected classified leukodystrophies; (c) identify the best symptomatic approaches for care to define a standard of care; and (d) assess the clinical validity and utility of next-generation sequencing in the leukodystrophies. It is expected that studying these diseases will also expand our understanding of myelin structure and myelination, and eventually help lead to effective treatment of these devastating disorders. These patients will be characterized by a combination of clinical, biochemical, pathological, and genetic methods.

Specific Aim 1. **To collect detailed clinical characterizations, including histories, physical examinations, symptomatic management, standardized assessments including patient reported outcomes, biochemical tests, genetic studies, neurophysiologic and neuroimaging studies in patients with both known and unsolved leukodystrophies to better comprehensively characterize such patients and obtain comparative clinical profiles.** These approaches will be pursued longitudinally. A broad spectrum of patients with both known and unsolved heritable white matter disorders of the brain will be evaluated under this protocol, including, among others:

- Leukodystrophies with a known molecular or biochemical cause
- Hypomyelination disorders of unknown cause
- White matter disorders with cerebral calcifications of unknown cause
- White matter disorders with cerebral cysts of unknown cause
- White matter disorders with brainstem tract abnormalities of unknown cause
- White matter disorders suspected to be caused by an inborn error of metabolism
- White matter disorders suspected to be caused by a chromosomal abnormality

Since the population of patients with leukodystrophies of unknown cause is heterogeneous, a comprehensive characterization of patients will allow for the clinical, biochemical or neuroradiologic diagnosis to be made when attainable. For those patients with an undiagnosed leukodystrophy this standardized characterization will allow for precise correlation with other patient profiles. We expect that, with time, patients within these categories will aggregate into new clinico-pathological groups. This nosology will facilitate continued biochemical and genetic research into these leukodystrophies. Additionally, longitudinal studies obtained through the course of routine clinical care will help define the unknown natural history of most leukodystrophies and identify future clinical outcome markers and best standards in leukodystrophy symptomatic management.

Specific Aim II. **To collect and bank excess clinical samples in subjects with known and unsolved leukodystrophies to develop a biorepository of excess clinical samples obtained when etiologic or health maintenance testing is performed and to assay these samples using established research methodologies.** The over-riding hypothesis of this aim is that integrated biochemical, genomic, metabolic, histologic and immunologic profiles of patients with leukodystrophy will define downstream pathway changes consistent with primary defects causing white matter disease. Urine, serum or plasma will be obtained when these biologic samples are obtained for clinical reasons. Fibroblasts will be obtained from cultures banked for clinical reasons or for the express purpose of obtaining patient cells for analysis of identified candidate genes and or the creation of cell lines including iPS (induced pluripotent stem) cells. Peripheral blood cell types will be obtained when venipuncture is performed for clinical reasons. Cerebrospinal fluid will be obtained from excess samples after lumbar puncture is obtained for clinical reasons. If tissue samples obtained for clinical reasons or post mortem are available they may also be banked. A blood sample may be requested for the purpose of providing a DNA sample. A Saliva sample may be obtained for the express purpose of obtaining a DNA sample. Finally banked or prospectively collected filter paper blood samples may be collected. Samples

banked in this fashion will be submitted to selected analyses including histologic, immunologic, genomic, proteomic, and biochemical approaches for the purpose of identifying changes that may help determine the molecular etiology or downstream changes related to the mechanism of disease.

Specific Aim III. **To maintain a longitudinal collection of data on disease presentation, progression, morbidities and the therapeutic interventions in leukodystrophy patients.** For most leukodystrophies, the natural disease course include age at presentation, features of disease, long term complications and standard symptomatic management and their impact are unknown. This aim will review and record patient reported outcomes as well as clinical records to create a longitudinal dataset of these features. Patient information will be collected in a robust data collection system, NeuroBANK™ (see details below) to ensure patient confidentiality, reliable integration of data from multiple providers and the ability to track data over time.

Specific Aim IV. **To investigate the diagnostic efficacy, clinical utility, and cost effectiveness of NGS for leukodystrophies by determining if NGS improves diagnostic effectiveness in the leukodystrophies relative to current diagnostic approaches and whether NGS results in changes to health care related costs.**
We propose an investigation of a subset of leukodystrophy-affected patients at the time of initial confirmation of MRI abnormalities, with prospective collection of patients randomly ascertained on a first come first served basis from a network of expert clinical sites. Subjects will undergo WGS in parallel to standard clinical testing in a staggered fashion unless a diagnosis achieved through standard clinical approaches. This approach aims to assess the diagnostic validity and utility of NGS approaches, with primary outcome measures including time to diagnosis and obtaining a diagnosis. Secondary outcomes will include number of visits required for diagnosis, invasive testing used for diagnosis, diagnosis-associated changes in medication (either stopping or starting medications), diagnosis-associated changes in providers, and diagnosis-related charges (including physician visits). We anticipate that findings from this approach will serve as a pilot for similar approaches in other rare disease cohorts, to establish the utility of WGS as a first line diagnostic tool for patients with suspected genetic conditions.

These goals will be best met using a collaborative approach and thus this study will implement a multi-site consortium approach to collect data and sample from a broad series of geographical sites to capture sufficient numbers of patients to achieve the stated goals. Taken together, these investigations hope to provide fundamental knowledge improving the diagnosis and care of patients with leukodystrophies.

B. Background and Significance

Leukodystrophies are genetic diseases that predominantly affect brain white matter, and constitute a significant proportion of the hereditary disorders of brain. Good progress in research into the leukodystrophies has been made, yielding new diagnoses in many disorders, increased understanding of the pathophysiology of known disorders and effective therapies for some disorders. However, many patients with progressive white matter diseases do not fit the criteria of any defined leukodystrophy and have no known etiology. In the past 5 years, of the patients with white matter disease of unknown cause we have evaluated at Children's National, fewer than 46% had no specific diagnosis after extensive clinical testing. This remaining group of patients offers the opportunity to describe novel disorders and provide improved diagnostic tools. Even

when a diagnosis is achieved, the diagnosis takes an average of eight years[2] and this "odyssey" results in testing charges to patients and insurers in excess of $8,000 on average per patient, including the majority of patients who never achieve a diagnosis at all (Richards et al, in press). These diagnostic challenges represent an urgent and unresolved gap in knowledge and disease characterization, as obtaining a definitive diagnosis is of paramount importance for leukodystrophy patients [3]. Leukodystrophies are currently diagnosed using cranial Magnetic Resonance Imaging (MRI) followed by sequential targeted genetic testing, [4] however next generation sequencing technologies offer the promise of more rapid and cost efficient approaches. In addition, some leukodystrophies have been classified, but have no genetic cause and in other known leukodystrophies, an identified gene has revealed little information about pathophysiology. This group offers the opportunity to improve understanding of the cause of disorders affecting central nervous system myelin. We propose to prospectively collect clinical data, bank laboratory samples in unclassified or poorly understood leukodystrophies, and utilize next generation sequencing approaches to aid in diagnosis of undiagnosed patients. We anticipate that this will assist in defining new disorders, establishing more rapid and efficient testing techniques, and developing mechanistic hypothesis of the pathophysiology of known disorders. Additionally, there is limited natural history data on most leukodystrophies and best standards of care are unknown in these conditions, despite their significant morbidity, mortality and health care costs.[5-7] Thus, these approaches will also focus on establishing the typical age of onset, presentation, morbidities, mortality and current symptomatic approaches in leukodystrophies and their subsets.

B.1 Unclassified Leukoencephalopathies

In the patients with white matter disease whose leukoencephalopathy remains unclassified after traditional clinical testing, several subgroups have emerged of interest (Table 1). These include the hypomyelinating leukoencephalopathies, the leukoencephalopathies with calcifications, the leukoencephalopathies with cystic changes and leukoencephalopathies with specific MRI patterns of brainstem tract involvement. Each of these categories currently has a limited differential diagnosis, and many patients remain without a specific diagnosis. Patients with clinical and radiologic criteria fitting into these categories are of special interest in describing novel disorders.

Table 1. Categories of unclassified leukodystrophies
Hypomyelinating leukoencephalopathies
Calcifying leukoencephalopathies
Leukoencephalopathies with cysts
Leukoencephalopathies with brainstem tract abnormalities on MRI

B.1.1 Hypomyelinating leukodystrophies are distinguished from other leukoencephalopathies by their characteristic lack of myelin development over time. Typically, white matter changes are homogeneous and confluent, with T2 signal hyperintensity, and normal or isointense signal on T1 weighted images. A characteristic disorder with hypomyelination is Pelizaeus Merzbacher disease. Other disorders within the differential diagnosis included Salla disease, 18q- syndrome [8,9] (haploinsufficiency of myelin basic protein or MBP). Recently, a number of other disorders with hypomyelination have been described, including HCC (hypomyelination with congential cataracts)[10-12], Pelizaeus Merzbacher like disease (associated with *GJA12* mutations)[13,14], 4H (hypomyelination with hypogonadotrophic hypogonadism and hypodontia)[15], HABC (hypomyelination with atrophy of the basal ganglia and cerebellum)[16]. Despite these advances, a large number of patients with hypomyelination remain without a specific diagnosis after an extended evaluation. In these patients, systematic evaluations to exclude known causes and

detailed clinical investigations to describe patients with unclassified disorders will hopeful yield novel diagnoses.

B.1.2 Calcifying leukodystrophies present a similar enigma. Calcifying leukoencephalopathies are those in which extensive changes in the cerebral white matter are accompanied by cerebral calcifications. A good example of a calcifying leukodystrophy is Aicardi Goutieres Syndrome (AGS). In AGS patients with typical clinical features (elevated CSF alpha interferon and pleocytosis along with characteristic brain calcifications), a large percentage now have mutations in established causative genes *AGS1-5*[17-19]. However, there remain patients who have no defined molecular etiology despite characteristic clinical findings. In addition, a number of other disorders with cerebral calcifications have been described, but have no known etiology, including cerebroretinal microangiopathy with calcification and cysts (CRMCC)[20-22]. Again, systemic evaluation of such patients may yield nosological groups and definition of novel disorders.

B.1.3 Cystic Leukoencephalopathies are yet another discrete group in which a large proportion remain without a specific diagnosis. Megalencephalic Leukoencephalopathy with subcortical cysts (causative gene *MLC-1*)[23-26], is one such disorder, although a proportion of patients with characteristic clinical findings have no mutations in *MLC1*[27]. Other disorders, such as mitochondrial cytopathies, can be suspected in this group of patients, but etiology often remain elusive.

B.1.4 A final category is leukoencephalopathies with brainstem tract involvement. A number of these unclassified leukoencephalopathies may be consistent with mutations in nuclear mitochondrial genes, as evidenced by the MRI abnormalities found in disorders with mutations in *SURF1*[28-31] and in LBSL (Leukoencephalopathy with brainstem and spine with elevated lactate)[32,33]. However, other categories of disorders can also present with striking abnormalities of the brainstem tracts, including ADLD (autosomal dominant leukodystrophy) caused by duplications in the gene for Lamin B1[34]. The differential diagnosis of patients with leukoencephalopathy and brainstem tract involvement on MRI remains poorly described and few diagnostic options are available.
Together, these unclassified leukoencephalopathies represent a not insignificant proportion of patients with heritable disorders of the white matter of the brain. Further research to better classify these groups would likely provide new diagnostic tools and improved understanding of myelin homeostasis.

Table 2.

Leukoencephalopathy	Cause	Biomarker	Pathophysiology
Hypomyelination with congential cataracts (HCC)	Mutations in the gene for hyccin	None, genetic testing only	Not understood
Hypomyelination with atrophy of the basal ganglia and cerebellum (HABC)	unknown	None, MRI pattern recognition only	Not understood
Hypomyelination w/ hypogonadotrophic hypogonadism and hypodontia (4H)	unknown	None, sural nerve biopsy only	Not understood
AGS without mutations in *AGS1-5*	unknown	None, clinical diagnosis	Not understood

Cerebroretinal microangiopathy with calcification and cysts	unknown	None, MRI pattern recognition only	Not understood
Adult Onset Leukodystrophy with Neuroaxonal Spheroids	unknown	None, clinical and MRI pattern recognition	Not understood

B.2 Classified leukoencephalopathies of unknown or poorly understood cause
A number of classified leukoencephalopathies have been identified, but may have no known cause, no biomarker or poorly understood pathophysiology (A non exhaustive list is supplied in Table 2). These leukoencephalopathies, while grouped as specific entities, may not have a specific marker permitting diagnosis, other than characteristic clinical or radiologic features. In those that have a molecular or biochemical test, there is no mechanistic hypothesis regarding the pathophysiology. Further clinical characterization of these disorders and collection of research samples, may permit future hypothesis driven studies to increase our understanding of their pathogenesis.

B.3 Classified Leukodystrophies with unknown disease progression and best standard of care symptomatic management. Even for the best characterized leukodystrophies, there is little understanding currently of their natural history and the best symptomatic management. Collaborators within our group are actively identifying those morbidities that might be preventable with ideal symptomatic management as well as their health care burden and costs.[5-7] However, much remains to be done to validate the disease progression, preventable complications and best standard of care in leukodystrophies (see Appendix F.a- The Symptomatic Management of Leukodystrophy Patients) in order to best optimize clinical care in these conditions.

B.4 Assessing the clinical validity and utility of next-generation sequencing in unclassified Leukoencephalopathies (LEUKOSEQ)
Next-generation sequencing (NGS) technologies have the potential to revolutionize the diagnostic process for rare disease, in particular leukodystrophies where the rate of diagnosis is historically so low. Our international working group (spearheaded by Drs. Vanderver, Taft, Bonkowsky, Bernard, Schiffmann and van der Knaap) has extensive and globally recognized expertise in deciphering the genetics underlying unsolved leukodystrophies. They collectively have been the largest contributor to the modern understanding of leukodystrophies etiology and pathobiology. This body of work over the last decades includes the description of Vanishing White Matter Disease (*EIF2B1-5*),[35-37] 4H syndrome (*POL3RA and B*),[15,38,39] Leukoencephalopathy with Brainstem and Spinal Cord Involvement and Lactate Elevation (*DARS2*),[33,40] Megalencephalic Leukoencephalopathy with subcortical Cysts (*MLC1 and HEPACAM*),[26,41] Leukoencephalopathy with Thalamic involvement and Lactate and Slow Improvement (*EARS2*).[42,43]
Since 2012, however, the pace of discovery has increased at a remarkable rate due to the use of whole genome sequencing (WGS) and whole exome sequencing (WES). This includes the discovery of a novel leukodystrophy, Hypomyelination with Brain stem and Spinal cord involvement and Leg spasticity (HBSL) which is caused by mutations in *DARS*,[44] and the finding that Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum (H-ABC) is caused by *de novo TUBB4A* mutations.[45] Finally, our group has performed the first cohort analysis of WES in leukodystrophy, with a diagnostic efficacy in the unsolved patients of nearly half, decreasing the proportion of unsolved cases from 50% to approximately 25% of all leukodystrophy patients.

Despite these advances in diagnostic efficacy, there are still significant issues in implementation of NGS in a clinical setting. Firstly, sample cohorts demonstrating diagnostic efficacy remain small, retrospective and open to possible ascertainment bias, limiting the interpretation of analytic utility (how efficient the test is at making a diagnosis). Second, there is no prospective information about impact on clinical management (whether the test results in different clinical monitoring, a change in medications, or alternate clinical interventions). Better understanding of the clinical validity and utility of such testing may help to implement appropriate testing within a clinical setting.

C. Preliminary Studies

C.1 Use of a comprehensive evaluation paradigm to diagnose novel leukodystrophies and explore known leukodystrophies

The approach described in this protocol has previously been successful in identifying patients with leukodystrophies belonging to novel nosologic groups and identifying biomarkers/providing improved understanding of existing leukodystrophies. The paradigm applied in the last few years under this existing protocol has advanced research in Childhood Ataxia with CS Hypomyelination/Vanishing White Matter (CACH/VWM) disease[46,47], Aicardi Goutieres Syndrome[19,48], Alexander disease, and novel previously unclassified hypomyelinating leukodystrophies including *TUBB4A* related H-ABC (Hypomyelination with atrophy of the basal ganglia and cerebellum), DARS associated leukodystrophy and Pol-III related leukodystrophy [38,44,45,49,50].

The clinical manifestations of white matter disease are protean and no single evaluation tool is sufficient to distinguish them. A detailed clinical evaluation remains important, however, as is seen in 4H (in which a clinician noted hypodontia and the lack of development of secondary sexual characteristics) and HCC (in which the salient clinical feature is congenital cataract). For this reason, examination by clinicians experienced in evaluating patients with leukodystrophies is useful in excluding known leukodystrophies and in describing potential novel disorders, and where possible patients will be clinical evaluated by an investigator on this protocol, and where this is not feasible clinic notes will be reviewed.

MRI pattern recognition is an important tool in classifying leukoencephalopathies. Advances in neuroimaging technology have greatly facilitated and simplified the diagnosis of a number of leukodystrophies. Specific MRI patterns have allowed the classification of several of the most recently identified leukodystrophies, CACH/VWM[37] and Megalencephalic Leukodystrophy with subcortical Cysts (MLC)[51-55]. Similarly, with the aid of MRI, new leukodystrophies will continue to be identified. These include LBSL[33,56] in which MRI identification led to genetic studies identifying a causative gene. In further examples, such as HABC[57] and 4H[15] (identified in the context of a similar protocol used in the NINDS), MRI classification has permitted identification of discrete leukodystrophies even if a genetic cause has not yet been elucidated. Thus, in this protocol, copies of all relevant imaging will be solicited and reviewed.

EMG/ NCS and possible nerve biopsies can be performed as part of the clinical evaluation of patients with leukodystrophy, reflecting the frequent involvement of the peripheral nerve myelin in leukoencephalopathies. In certain disorders, such as 4H, nerve biopsies are diagnostic of an individual leukoencephalopathy[15]. Other tests, such as EEG, neuropyschologic testing, rehabilition evaluations, ophthalmologic evaluations, and other specialty evaluations, are part of a standard diagnostic evaluation. In all cases results of this testing, and other clinical evaluations may be requested and reviewed.

Blood, urine and skin biopsy testing may be obtained in a standard clinical fashion as part of the evaluation of a patient with a leukodystrophy. When performed, results of immunologic, biochemical, chemistry, hematologic and other standard clinical testing will be reviewed. Where excess samples are available, these will be banked. Additionally, a blood sample may be performed to obtain research samples.

Cerebrospinal fluid (CSF) is an important biologic fluid and is part of the routine clinical evaluation of patients with unclassified leukoencephalopathies. Routine studies such as cell count, glucose and protein evaluations are part of the detailed evaluation of a neurologic disorder. In the case of the hypomyelinating leukoencephalopathies, cystic leukoencephalopathies and encephalopathies with brainstem involvement, CSF can be used to exclude mitochondrial disease (lactate), and in the case of the calcifying leukoencephalopathy[58-60] and hypomyelination[61,62], CSF is necessary to assess for inflammatory disorders (alpha interferon, neurochemistry). They are also important for future studies and biomarker development, as seen in CACH/VWM. Thus, when performed for clinical reasons, results of CSF analysis will be reviewed and an aliquot of excess sample will be stored.

Biologic samples will be studied using histologic, immunologic, biochemical, genomic and proteomic applications, as consistent with the suspected underlying mechanism. These studies will serve to inform later mechanistic approaches to disease study. The Principal Investigator has experience in these methodologies, including but not limited to immunohistochemistry, western blot, RT-PCR, high throughput sequencing, standard sequencing, array technologies, proteomic applications and mass spectrometry small molecule analysis.

Leukodystrophies are systemic genetic disorders with predominant nervous system white matter manifestations. Their complex clinical presentations and heterogeneous etiologies make their diagnosis challenging. Available biochemical, genetic, and neuroimaging techniques are still unable to provide a diagnosis in a significant proportion of leukodystrophies. There is therefore a need for continued efforts in the diagnosis of leukodystrophies. There is a need to classify leukodystrophies to better understand their pathophysiology, aid in prognosis and remediation, develop new therapies and assess efficacy of treatment.

C.2 Use of a comprehensive evaluation paradigm to establish the natural history and standards of care in the leukodystrophies.

A consensus of experts recently identified key medical complications seen in leukodystrophy patient (Appendix R- The Symptomatic Management of Leukodystrophy Patients These include respiratory complications including from aspiration events, motor complications and cognitive decline, among others (Table 3). These complications will be specifically tracked at each clinical visit for each individual, including age of onset, outcomes and clinical directed management chosen by the caring physician (Appendix D.a: Clinical Outcomes).

Table 3. Established complications in Leukodystrophy Patients

Established Complications	**Many Serious medical complications are treatable and potentially preventable**
Cognitive dysfunction and decline	Anxiety/depression
Constipation	Chronic pain
Dystonia	Iatrogenic sedation
Hearing and language impairment	Joint dislocation/fracture
Scoliosis	Malnutrition
Sialorrhea	Pneumonia
Sleep Disturbance	Pressure sores/wound infections

Spasticity	Urinary tract infections
Visual Impairment	

D. Research Design and Methods

D1. Specific Aim 1. **To collect detailed clinical characterizations, including histories, physical examinations, biochemical tests, genetic studies, neurophysiologic and neuroimaging studies in patients with both known and unsolved leukodystrophies to better comprehensively characterize such patients and obtain comparative clinical profiles.** Patients will be referred both from within and from outside the institution. If interested, prospective participants will call the PI/co-PIs/co-investigators, who will review the informed consent with the prospective participant and the prospective participant will be invited to come to one of the participating sites for a clinical evaluation by the PI, Co-PI, or qualified Co-Investigator. Detailed clinical information will be collected and recorded in consented patients via NeuroBANK™ according to standardized data collection forms (Appendices A.a-A.e). These will be analyzed in a descriptive fashion to identify novel nosologic groups to identify novel disorders within the unsolved leukodystrophies. Additionally, online password protected databases, such as Redcap will be used to collect referral information prior to inclusion of consented patients in NeuroBANK.

D1.1) Rationale and experimental approach. A comprehensive characterization of patients will allow for the clinical, biochemical or neuroradiologic diagnosis to be made when attainable. For those patients with an unsolved leukodystrophy this standardized characterization will allow for precise correlation with genomic/proteomic profiles obtained in Specific Aim II and comparison to clinical profiles of patients with known leukodystrophies. For this reason, review of the clinical care of the patient with a leukodystrophy will be approached in a standardized fashion (see appendices C.a – C.g). Previous and ongoing evaluations including standard biochemical, genetic, neurophysiologic and neuroimaging studies will be reviewed. Patients will be entered into a custom database featuring all elements of the characterization and grouped as having a known or unclassified leukodystrophy via NeuroBANK™ (see section D3.3 for full description of this platform).

D1.2) Methods for Clinical Characterization

D1.2a. Patient Enrollment: Patients with leukodystrophies will be referred from within a participating institution or from outside collaborating institutions for inclusion in the study. Outside physicians who have submitted samples to the PI for previous studies of leukodystrophy will be contacted by letter to inform them of the proposed study. Lab directors whose labs perform genetic testing for select genes related to leukodystrophy will be asked to provide information about this research to referring physicians (see recruitment materials). Additional procedures for recruitment may include the Myelin Disorders Bioregistry website (www.myelindisorders.org) or database generated surveys to referral families such as Redcap Survey® or Patient Reported tools such as those included in NeuroBANK™. In addition, study information (title of study, PI, contact information) will be posted on www.genetests.org. Outside physicians who believe their patients are eligible will be asked to provide patients with contact information for the PI/co-PIs/Co-Investigators/study coordinator. If interested, prospective participants will call the PI/co-PIs/Co-Investigators/study coordinator.

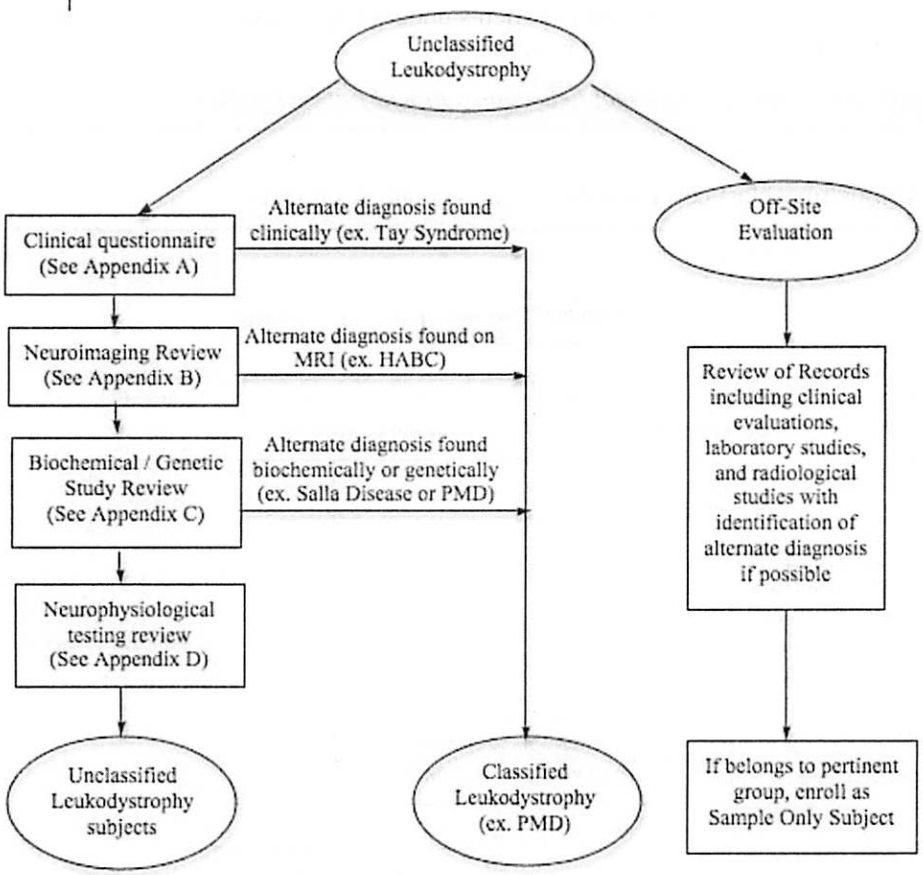
Informed consent will be mailed/ or available online to prospective participants and reviewed over the phone prior to signing for participants not coming to a study site for clinical evaluation and will be completed in person by all participants coming to a study site for clinical evaluation. Patients who wish to enroll from outside a study site will be sent an instruction sheet for how to enroll, send samples, and how to arrange a clinic visit (see Appendix E.a). When possible every effort will be made for this clinical evaluation to include a neurologic exam by the PI or qualified co-investigators in addition to a comprehensive chart review. When it is not possible for the PI/co-PI/Co-investigator to conduct a

neurologic exam, records of previous neurologic exams will be requested in addition to other medical records.
To accomplish this evaluation, patients will be interviewed and examined as part of a standardized neurologic assessment (see Appendix A.a). Elements of history and examination pertinent to the diagnosis of a leukodystrophy will be recorded in a database. Available neuroimaging, neurophysiologic, biochemical and molecular data for individual patients will be reviewed and recorded (for standard MRI evaluation see appendix A.b, for standardized neurophysiologic evaluation see appendix A.c, for standardized biochemical and mutation analysis see appendix A.d). Records will be requested for any biochemical and molecular studies performed as part of clinical care. Patients who have lumbar puncture, skin biopsy, urinalysis and venipuncture as part of their clinical care will be asked to donate **samples** for the purposes of this research study. If tissue specimens are obtained for diagnostic purposes or as part of post mortem studies, these may b e requested for banking and study. A blood sample may be obtained for the specific purpose of collecting a DNA sample, other blood samples or banking a filter paper blood sample. A saliva sample may be collected for the specific purpose of collecting a DNA sample. The PI expects to recruit >50 patients a year based on recent referrals the Myelin Disorders Bioregistry Project for analysis of genes affected in leukodystrophies.

In addition, healthy relatives may have blood or saliva collected for genomic applications. All such subjects will sign informed consent or assent as applicable. No PHI will be collected for these subjects and a unique identifier linking them and their relationship to the proband will be created.

Finally, in some cases, patients with medical records, MR or CT imaging, may have great educational relevance, but consent may not be feasible, either because the patient was not originally a study participant (patients seen for clinical evaluation) or because the patient is deceased or lost to follow up. In these cases, de-identified records, MRI or CT images will be used for educational and publication purposes, with no PHI attached. The images will be de-identified using eFILM® software to remove name, date of birth, date and location of study and referring physician, such that the DICOM images with this information will not be able to be retrieved. These images will be stored in a password protected MRI database removed from all other identifying information about the subject. A waiver of documentation of informed consent is provided for these subjects.

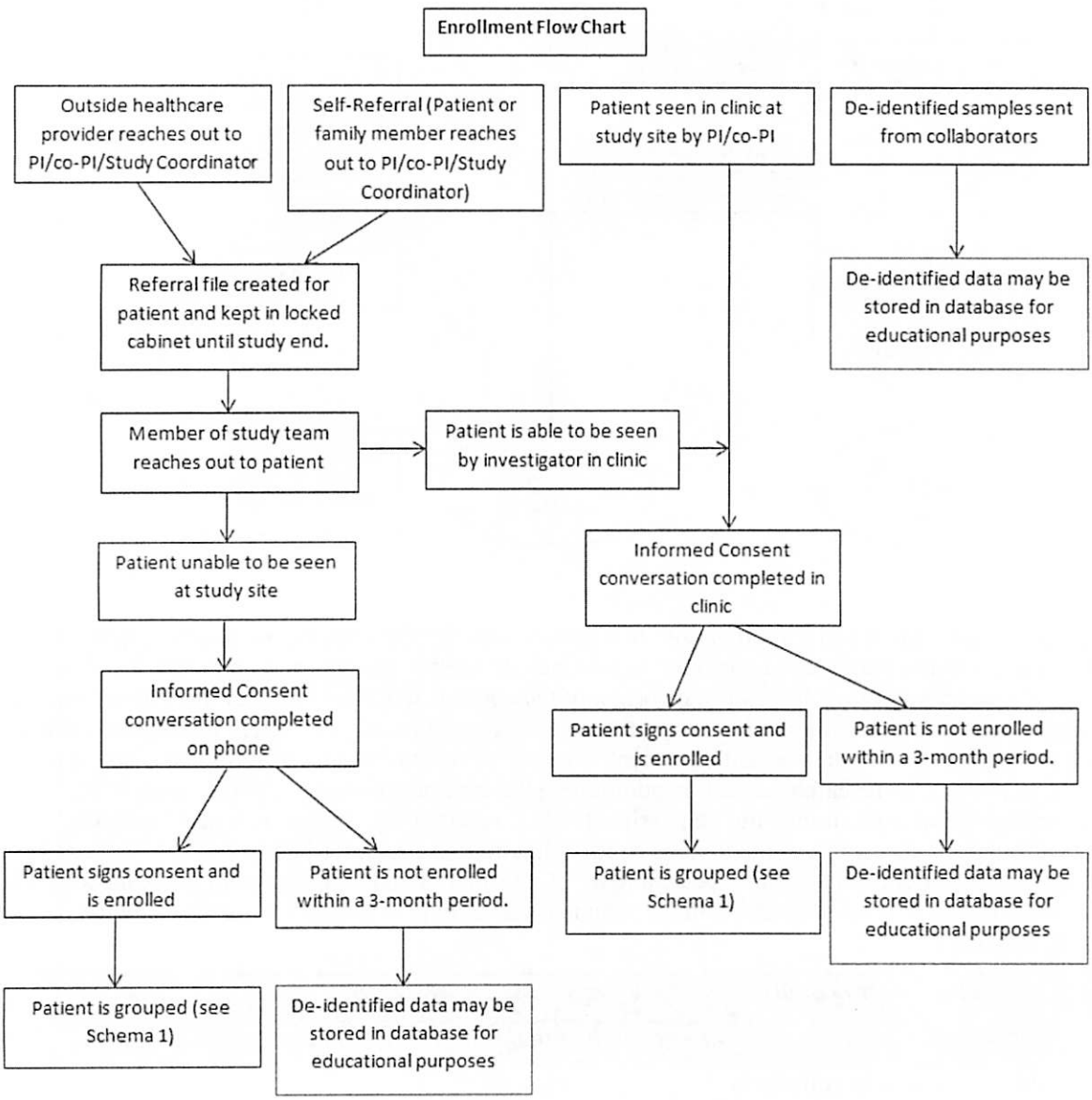
Schema 1: Clinical Characterization



D1.2b. Control Enrollment and Classification: In addition to the patients having a leukodystrophy, the study will enroll control subjects. These controls will include healthy patients and patients with other neurologic disorders involving the brain. The origin of the controls will vary based on the type of sample considered. Because all samples will be de-identified and because the only document linking the patient PHI with the sample will be the consent document, a waiver of documentation of informed consent is the best option to protect the research subject. In addition, in the case of pre-existing tissue banks (fibroblast cultures, cerebrospinal fluid) it may not be possible to obtain consent for tissues with no identifying medical information. Examples of the various control situations are as described in Table 4. Patients with whom there is direct contact will receive a letter of information that is included in the Appendix. The only information that will be collected with the sample is age at time of collection, gender, ethnicity and underlying diagnosis.

Table 4. Examples of control subjects
In the case of peripheral blood cells(consent will be sought for group 1 and group 2)
1) healthy adult family volunteers
2) patients with other non progressive disorders affecting white matter (periventricular leukomalacia, brain tumor) when undergoing standard, clinically indicated venipuncture.

In the case of cerebrospinal fluid (consent will not be sought for group 1, will be sought for group 2)
1) pre-existing banks of cerebrospinal fluid of patients with traumatic brain injury, brain tumor, aseptic meningitis or other neurologic disorders (anonymous samples). 2) excess samples of cerebrospinal fluid in patients undergoing evaluation for central nervous system infection or for idiopathic intracranial hypertension
In the case of fibroblasts (pre-existing specimens, consent will not be sought)
Banked anonymous fibroblast cell cultures of healthy control subjects



Schema 2. Schematic of Study Enrollment

D1.3 Analysis Plan: In order to characterize the clinical features of the different types of leukodystrophies, we will compare the various known leukodystrophies and the unknown leukodystophies based on either analysis of variance and covariance for measurement outcomes or contingency table analysis or logistic regression for categorical variables. T- of F-statistics will be used to identify statistically significant differences in the means between groups and chi square values will be used to identify statistically significant differences in the frequency of categories between groups. This analysis will help us identify those factors that are common to many or all forms of leukodystrophies and those that may be unique to the unclassified forms. We will pay particular attention in subsequent analyses to those features that are distinctive among the groups. Subsequent analyses will employ two distinct methods of data reduction, one statistical, exploratory factor analysis, and one heuristic, neural network analysis, to attempt to define subtypes based on clinical features within the unclassified group. By comparing the results of the two methods, we will be able to identify those subtypes for which there are an are not agreement between the different methods.

Statistical Power: Power assessments are derived based on two tailed type 1 error of 0.05%. When we compare measurements between groups of 50, we will be able to detect moderate 0.55 sd effect size differences between groups with 84% power and are virtually certain to detect effect sizes differences of 0.8 sd. For comparisons involving differences in proportions between groups, we will be able to detect roughly 2-fold differences with 80% power in factors whose prevalence is between 20% to 35%. The data reduction/classification steps are viewed as hypothesis generating and thus have not subjected to power analysis.

D1.4) Anticipated results, pitfalls and alternatives We expect to recruit a sufficient number of patients with leukodystrophies and to adequately categorize them with the described methods. However, in view of the fact that these disorders are rare, it is possible that by referral from within our institution and collaborating institutions, we will not recruit sufficient numbers of patients with unclassified leukodystrophies to generate statistically significant results. In that case, we will advertise the study via professional meetings and associations. It is also possible that the methods used to categorize patients are incomplete. As new diagnostic tests become available, or as our knowledge of pertinent elements of history increases, we will add these factors to the described methods of diagnosis or characterization.

D2. Specific Aim II. **To collect and bank excess clinical samples in subjects with known and unsolved leukodystrophies to develop a biorepository of excess clinical samples obtained when etiologic or health maintenance testing is performed and to assay these samples using established research methodologies.**

D2.1) Rationale and experimental approach: The application of state-of-the-art techniques to patients with undiagnosed white matter disease has many potential benefits. Establishing pathogenesis specific histologic, immunologic, biochemical, genomic or proteomic profiles for inherited disorders of the white matter disease would help classify unsolved leukodystrophies and help further etiologic study. Disease specific biomarkers for neurodegenerative white matter disease would help differentiate between a static white matter injury (perinatal, infectious or other) and a slowly progressive leukodystrophy.

Genomic applications, including gene expression profiling, standard sequencing, RT PCR, are largely established techniques that have proven utility in identifying novel leukodystrophies and their molecular cause. Similarly, biochemical, immunologic and histologic studies have demonstrated utility in the diagnosis and research of many well established leukodystrophies. Proteomic studies have only recently become efficient enough for applications such as the proposed study. The use of cerebrospinal fluid in the study of leukodystrophies is ongoing in our laboratory, however and so we expect to be able to use these emerging techniques successfully as part of this study. Similarly, next gen sequencing approaches are novel in their application to leukodystrophies.

D2.2) Experimental Methods- Patient selection: Patients will be classified as described in Specific Aim I, D1.2b. Samples collected under specific aim I will be analyzed by selected techniques, including histologic, immunologic, genomic, proteomic and biochemical approaches. Studies will be performed on excess patient samples obtained during standardized diagnostic evaluation of patients with leukodystrophies. They will be obtained in some cases as a part of appropriate patient care and some cases (blood, saliva) for the purpose of this study. It is expected, however, that adequate blood, CSF, urine or tissue samples will be available, after performing clinically indicated studies, for projected studies. A blood sample may be requested for the purposes of DNA collection and analysis. Control samples as collected above will be tested according to similar paradigms. Blood samples will be collected only to the maximum of 3cc/kg in a single draw, with no more than 7cc/kg over 6 weeks, total less than 450cc. For participants over 10kg this will permit collection of two 6cc EDTA, one 6cc red top, one 6cc green top, and one 2.5cc PAXgene tube (total blood = 26.5cc). For participants under 10kg and more than 3kg this will permit collection of one 4cc EDTA and one 2.5cc PAXgene (total blood = 6.5cc).

D2.3) Experimental Methods- Sample collection

D2.3a. Peripheral blood cell collection The blood sample size will be based on a formula the laboratory at the applicant's institution has used successfully for genomic studies in the past. Based on past experience isolating WBC subsets and an expected average WBC count of 10,000 cells/μL (10,000,000 cells/mL), each whole blood sample will need to be around 6 mL, allowing for some waste. For each sample taken, the applicant will collect and bank monocytes and T cell lymphocytes. Monocytes and T cell lymphocytes are isolated immediately after blood draw using StemCell Technologies "RosetteStep" negative cell separations. Negative (rather than antibody-mediated positive cell selections) are critical to avoid activation of the cells being isolated. In addition, plasma samples will be banked as residual samples from the peripheral blood cell collection.

D2.3b.Fibroblast cell collection and culture Fibroblasts for cell culture will be collected as part of clinical care for the diagnosis of a patient with an unexplained neurodegenerative disorder. Skin biopsy for fibroblasts cell culture will be performed at the referring institution. In the case of patients with previously collected and established fibroblast cell cultures, cells will be requested as part of their evaluation. Control fibroblast cultures will be obtained from healthy banked tissue. Fibroblasts may be used in functional validation of identified genetic variants or for the generation of iPS cells.

D2.3c. CSF Sample collection Excess cerebrospinal fluid samples will be collected in patients with leukodystrophy after lumbar puncture is performed for diagnostic or research indications at the referring institution. Excess cerebrospinal fluid samples will be collected in controls with idiopathic intracranial hypertension (pseudotumor cerebri) requiring serial lumbar punctures for management of increased intracranial pressure or receiving an initial lumbar puncture for the exclusion of such a diagnosis. At least 15 new patients a year with this diagnosis are followed in the neurology clinic. Excess cerebrospinal fluid samples will also be collected in controls receiving lumbar punctures to exclude neurologic infection. Cerebrospinal fluid will be collected to a minimum requirement of 1cc. Any available excess cerebrospinal fluid will be banked. Fresh CSF samples will undergo standard a CSF panel to include white blood cell, red blood cell, protein, and glucose measurement as clinically indicated. Any samples contaminated by red blood cells will be centrifuged to remove blood contamination prior to storage. Samples will then be stored in aliquots at -80 degrees Celsius.

D2.3d Serum and plasma collection Serum and plasma will be processed from excess blood samples collected at the time of a clinically indicated venipuncture according to standard laboratory protocols and conserved at -80 degrees Celsius.

D2.3e Urine collection urine will be processed from excess clinical sample collected for clinically indicated reasons, filtered and conserved at -80 degrees Celsius.

D2.3f Saliva collections and whole blood collections for DNA and RNA extraction Saliva (collected using Oragene® kits) or whole blood (Quiagen® extraction kits and RNA extraction kits such as PAX gene tubes) will be used for DNA /RNA extraction and conserved at -80 degrees Celsius.

D2.3g Filter paper blood spot collection. During the course of venipuncture, filter paper blood spots may be collected and banked. Alternately, previously banked filter paper blood spots may be retrieved with parental consent and banked for studies of genomic material, mRNA or disease specific analytes.

All samples will be stored in dedicated freezer space using deidentified freezer safe label systems with barcode identification. Those samples (such as filter paper blood spots or paraffin embedded blocks or slides) able to be banked in non refrigerated settings will be kept in a locked cabinet.

De-identified samples may be shared with researchers in the U.S. or other countries to perform additional research, place it into research databases, or use it to improve the design of future studies. Anonymized fibroblast samples will be sent to collaborators, for establishment and research of human induced pluripotent stem (iPS) cells. If clinically relevant information is found or further information with regards to a sample is wanted by the outside researcher/institution, only approved study personnel will contact the participant. At no point will the outside researcher/institution have access to PHI of the participants.

D2.4 Experimental Method- Research Assays

Samples will be assayed according to techniques selected among standard laboratory manipulations, including histologic, immunologic, biochemical, genomic and proteomic techniques including the following: immunohistochemistry, histochemistry, cell culture and cellular based experiments, live cell imaging, ELISA, multiplex measurements of cytokines, chemokines, and antibody arrays, GC and LCMS small molecule measurement, Gene expression profiling, RT PCR, standard sequencing, next generation sequencing, western blot, 2D gel analysis, low molecular weight proteomics, shot gun proteomics.

D2. 5 Data Analysis Results of clinical and laboratory evaluations for both known and unsolved leukodystrophies will be analyzed in an ongoing fashion during this prospective clinical study. That will allow for description of potential disease specific profiles early in the course of the project and validation of results with a subset of study patients. Specific clinical characteristics of patients will be described as the anatomic localization of nervous system involvement on clinical exam, neurophysiologic studies and neuroimaging. Results of laboratory testing of serum, plasma, urine, saliva, peripheral leukocytes, CSF, fibroblasts, and other tissues will be described in the context of mechanisms of disease resulting in white matter disorders. Correlation of these specific clinical and laboratory profiles will be performed to identify disease specific profiles aiding in the diagnosis of unidentified leukodystrophies.

Power Analysis Since the study is generating hypotheses to be tested elsewhere there is less concern about false positive results. Therefore we have elected to emphasize repeatability rather than formal statistical testing in defining these hypotheses. Therefore, power and sample size has not been evaluated.

D2.5) Anticipated results, pitfalls and alternatives We expect this correlation to generate clinically useful results for the improved diagnosis of patients with leukodystrophy. However, in view of the limited number of patients with these disorders and the small sample size, it is possible that each patient with an unclassified leukodystrophy will represent a distinct clinical entity and that genetic/proteomic clusters will be sufficiently varied to limit forming associations. In this case, after analysis of the initial patients we will actively seek out patients with similar clinical pictures for genomic and proteomic testing. In addition, we will search analyses for patterns common to all the leukodystrophies in the aim of improving our understanding of the pathophysiology of these rare disorders and compare these to the control patients with non progressive white matter disorders with the aim of establishing diagnostic tools for leukodystrophies in general.

D3. *Specific Aim III.* To maintain a longitudinal collection of data on disease presentation, progression, morbidities and the therapeutic interventions in leukodystrophy patients.

D3.1 ***Rationale and experimental approach:*** For most leukodystrophies, the natural disease course include age at presentation, features of disease, long term complications and standard symptomatic management and their impact are unknown. This aim will review and record patient reported outcomes as well as clinical records to create a longitudinal dataset of these features.

Patient information will be collected in a robust data collection system, NeurobBANK™ to ensure patient confidentiality, reliable integration of data from multiple providers and patient reported outcomes and the ability to track data over time.

D3.2 Experimental Methods: Longitudinal Clinical Assessments

Clinical assessments will be used as in Specific Aim 1, with the same measurement and data collection tools, over the time course of the patient's disease. Data collection time points will be established in 6 month intervals, the typical minimal interval at which a leukodystrophy patient is seen clinically, in order to permit scheduling as per routine clinical approaches. Thus data can be collected on that patient anytime during the six month interval. In addition to the data collection points used in the initial assessment and during subsequent six month intervals, additional entries will be recorded when the patient has an event complicating the leukodystrophy, such as an unexpected hospitalization (such as for an aspiration pneumonia), or an anticipated event (such as an elective surgery for a gastrostomy tube placement). Finally, patient reported outcomes will be generated on standardized intervals (see Appendix D).

D3.3 Experimental Methods: Data Collection and Management

D3.3.1 Introduction to NeuroBANK™

NeuroBANK™ is a collaboration and data repository platform maintained by the Massachusetts General Hospital (MGH) Neurological Clinical Research Institute (NCRI). This platform facilitates:

1. Capture of clinical and research data from neurologic patients for individual projects in a structured and secure system;
2. Aggregating and sharing uniform, deidentified and/or anonymized datasets for secondary analyses.

Data Management (DM) at NeuroBANK™ is responsible for the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with applicable Sponsor and regulatory requirements. Site personnel will collect, transcribe, correct, and transmit the data onto source documents, Case Report Forms (CRFs), and/or other forms used to report, track and record clinical research data. DM is responsible for developing, testing, and managing clinical data management activities.

D 3.3.2.Data Entry and Checks

The site personnel are instructed to enter information into the NeuroBANK™ Electronic Data Capture (EDC) System.. Data capture is the responsibility of the staff at the site under the supervision of the Site Investigator (SI). During the study, the Site investigator must maintain complete and accurate documentation for the study.

The NeuroBANK™ platform provides password protection. An edit checking and data clarification process will be put in place to ensure accuracy of the data. Logic and range checks as well as more sophisticated rules may be built into the eCRFs to provide immediate error checking of the data entered. The system has the capability to automatically create electronic queries for forms that contain data that are out of range, out of window, missing or not calculated correctly. The sites will only have access to the queries concerning their subjects.

D 3.3.3 Data Lock Process

The platform will have the ability to lock the project-specific visits to prevent any modification of data once the project is closed. Once this option is activated, every user will have Read-Only access to the data.

D 3.3.4 Data Handling And Record Keeping

The Site Investigator (SI) is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. Data reported in the eCRF derived from source documents should be consistent with the source documents and discrepancies should be explained.

D 3.3.5 Confidentiality

The NeuroBANK™ software and patient data reside on servers located in the Partners Healthcare Systems (Partners) server farm. Physical and software access to the servers and security is provided by the Partners IT department. Members of the NeuroBANK™ management team will do everything, within reason, to keep a participant's identity protected.

D 3.3.6 Global Unique Identifier (GUID)

A patient Global Unique Identifier (GUID) will be used as the identifier for individuals participating in the study in NeuroBANK™. The GUID is an 11-character string that is generated using encryption technology and algorithms licensed by the NCRI from the National Institutes of Health (NIH).

The GUID is generated on a secure website that utilizes 128-bit Secure Socket Layer (SSL). Of note, this website is not linked to NeuroBANK™. The GUID is generated using an irreversible encryption algorithm – it accepts twelve identifying data elements, (e.g. last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth, etc.), and produces a unique random-generated character string, or GUID. No identifying information is stored in the system; it is simply used to generate the GUID. If the same information is entered again, the same GUID will be returned.

The GUID is entered into NeuroBANK™ when the patient is being created in the system. As the same patient may participate in multiple studies, NeuroBANK™ will also allow capturing a study-specific ID for the patient. For more information about NeuroBANK™ or the GUID, please go to: www.neurobank.org.

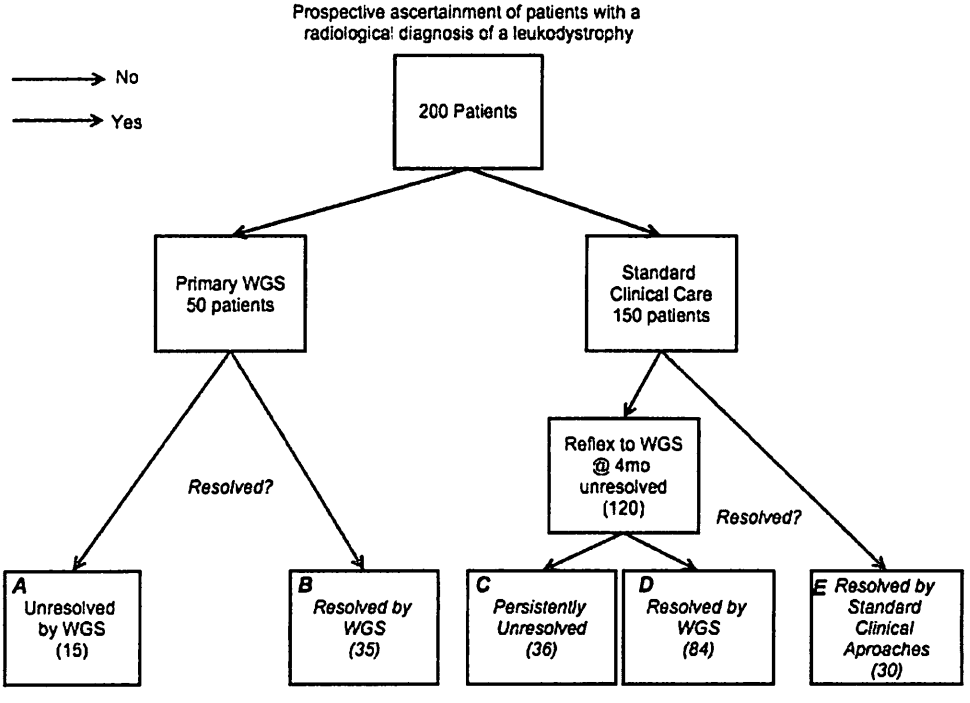
D3.4 Analysis Plan: In order to characterize the clinical features of the different types of leukodystrophies over time, we will compare the various known leukodystrophies and the unknown leukodystophies based on either analysis of variance and covariance for measurement outcomes or contingency table analysis or logistic regression for categorical variables. T- of F-statistics will be used to identify statistically significant differences in the means between groups and chi square values will be used to identify statistically significant differences in the frequency of categories between groups. This analysis will help us identify those factors that are common to many or all forms of leukodystrophies and those that may be unique to the unclassified forms. We will pay particular attention in subsequent analyses to those features that are distinctive among the groups. Subsequent analyses will employ two distinct methods of data reduction, one statistical, exploratory factor analysis, and one heuristic, neural network analysis, to attempt to define subtypes based on clinical features within the unclassified group. By comparing the results of the two methods, we will be able to identify those subtypes for which there are an are not agreement between the different methods.

Statistical Power: Power assessments are derived based on two tailed type 1 error of 0.05%. When we compare measurements between groups of 50, we will be able to detect moderate 0.55 sd effect size differences between groups with 84% power and are virtually certain to detect effect sizes differences of 0.8 sd. For comparisons involving differences in proportions between groups, we will be able to detect roughly 2-fold differences with 80% power in factors whose prevalence is between 20% to 35%. The data reduction/classification steps are viewed as hypothesis generating and thus have not subjected to power analysis.

D4. Specific Aim IV. **To investigate the diagnostic efficacy, clinical utility, and cost effectiveness of NGS for leukodystrophies by determining if NGS improves diagnostic effectiveness in the**

leukodystrophies relative to current diagnostic approaches and whether NGS results in changes to health care related costs (LEUKOSEQ).

Subjects will undergo standard clinical care according to existing algorithms based on MRI pattern recognition[63] while WGS is ongoing, and will be permitted to have clinical indicated testing including enzymatic, analytic or sequencing by single or targeted panels as considered appropriate by the expert clinician. This trial will have a pragmatic design, recognizing that the lack of standardization in leukodystrophy diagnostics in clinical care cannot be adapted to a strict trial design. Data will be analyzed according to a "first-to-diagnose" algorithm, with the first modality to provide a diagnosis accepted by an expert review panel and results provided to the clinical care team. Patients will also be studied for changes in delivered health care, including changes in defined comorbidities (aspiration and infectious pneumonia, seizures, changes in medications for management of spasticity and other non disease specific pharmacologic interventions, operative decisions, performance of invasive testing) as well as alterations in patient centered quality of life measures. These measures will be compared according to time marked analyses relative to the time of diagnosis. Finally, diagnostic related costs performed on a clinical basis will be studied relative to NGS costs. Data collection will also include additional costs due to downstream testing for validation of NGS related diagnosis in the patient and their family, as well as changes in health care related costs after diagnosis.



Schema 3. Schematic of NGS in Leukodystrophies (Leukoseq) trial. Hypothesized number of cases in each category in parentheses.

D4.1 LEUKOSEQ Inclusion criteria & initial patient assessment

D4.1.1 Patient selection: Subjects will be recruited from new patients seen at the clinical sites of the Centers of Excellence in Leukodystrophy and Leukoencephalopathy (CELLs). All patients and their families will

have full informed consent in collection of natural history data and NGS approaches by the central site. Eligibility criteria will include identification of a presumed leukodystrophy on MRI (Table 5). MRIs will be analyzed according to a publically available non computational algorithm accessible to even non expert child neurologists and geneticists. [63] Patients will be enrolled irrespective of the clinicians presumptive diagnosis (ie even if the clinician feels there is an unambiguous diagnosis based on MRI and initial clinical assessment, as long as no confirmatory testing has been performed and the time since identification of the leukodystrophy is <2 months. Patients will be randomized to either the primary WGS arm or Standard of Practice (SOP) arm with secondary WGS at four months (Schema 3). All patients will receive clinical WGS results unless a diagnosis is made using standard clinical means, by six months after enrollment. Centralized stratified permuted block randomization will occur to create balance between different testing sites to minimize the effect of differential expertise in current diagnostic approaches, as well as gender and age.
The submitting clinician will provide a full phenotypic description of the patient, including a standardized assessment and full clinical notes. The clinician will also score a pre-test probability of a specific diagnosis and of the likelihood of identification of a genetic diagnosis.
Selected patients will then be reviewed by a committee of leukodystrophy experts from the Global Leukodystrophy Initiative, namely Drs van der Knaap, Bernard, Wolf and Vanderver, who will define if there is a likely diagnosis based on MRI and clinical features and re-categorize subjects with pre-test probabilities.

Table 5. Eligible Patients for Leukoseq
Inclusion criteria: • Abnormalities of the white matter signal on neuroimaging (MRI) with T2 hyperintensity which must be diffuse or involve specific anatomical tracts consistent with a genetic diagnosis • Identified < 2 months prior to enrollment • No evidence of an acquired cause for the white matter abnormalities (infection, trauma, birth related injury) • No pre-existing diagnosis • Less than 18 years of age • Availability of both biologic parents for blood sampling
Exclusion criteria: • Acquired disorders, including infection, acute disseminated encephalomyelitis (ADEM), multiple sclerosis, vasculitis or toxic leukoencephalopathies • Patients with no third party payor health insurer and ability to receive standard of care diagnosis and

D4.1.2 Initial patient assessment and standard clinical approaches. Patients will undergo a thorough phenotypic assessment by a clinical expert in the leukodystrophies and clinical data and disease course will be recorded in a custom database. MRIs will be scored according to a standard data collection system in use in this patient population for several decades and classified according to a standard diagnostic algorithm by Drs van der Knaap, Bernard, Wolf and Vanderver. All patients will continue to undergo clinical evaluation, including one focused on disorders for which an existing therapeutic intervention exists (Table 6). Patients will then further undergo clinical diagnostic testing as ordered by a neurologist or geneticists with special expertise in leukodystrophy, excluding WGS, though targeted sequencing of genes based on MRI or clinical phenotype will be permitted. [63] A timeline of tests ordered will be created relative to the date of the diagnostic

MRI and first visit to the referral center. This data will be collected by comparison of patient reports that testing occurred and direct weekly contact with the practitioner during the four month period of standard diagnostic testing in the SOP cohort. Secondary outcomes including number of clinical visits and invasive testing (sedated MRI, lumbar puncture, skin biopsy) will also be recorded. If a specific molecular or definitive biochemical diagnosis is made by either WGS or clinical means, the patient will be considered as having achieved the endpoint of the diagnostic trial, which is a definitive diagnosis. All clinical test costs, except for the WGS being done through this study, will be billed to patient insurance as per current clinical approaches.

Table 6. Clinical Standard of Care Evaluation for Leukodystrophy and Leukodystrophy Mimickers

Part A. Limited initial testing in all subjects of both arms to exclude a disorder with a potential intervention and include Plasma Very Long Chain Fatty Acids, Leukocyte lysosomal enzymes for galactocerebrosidase and Arylsulfatase A, followed by more extensive testing according to clinical presentation:

Part B. Enzymatic or biochemical analytes- would be incremental and ordered based on clinical and radiologic phenotype	**Part C. Molecular testing in single genes or targeted panels**
Lactate, pyruvate Ammonia levels, plasma amino acids, urine organic acids Phytanic and pristanic acid Pipecolic acid and bile acids Cholestanol Isoelectric focusing of transferrin Galactose 1-phosphate Reverse T3 and TSH CPK Copper and ceruloplasmin Urine organic acids more specifically for N-acetylaspartic acid and L-2-hydroxyglutaric acid Urine oligosaccharides/ mucopolysaccharides assay, Urinary sulfatides Urine metabolites of leukotriene B4 Urine SAICA riboside and succinyladenosine (S-Ado) Urine sulfocysteine Urine amino acids CSF lymphocytosis, augmentation of INF-α, increased levels of pterins, CSF neurotransmitters, methyltetrahydrofolate, lactate, pyruvate. Possible fibroblast or leukocyte testing for deficient enzyme activity of aspartoacylase, Sterol 27-hydroxylase, α-fucosidase, Glycogen brancher enzyme (GBE), fatty aldehyde dehydrogenase(FALDH) and/or of fatty alcohol:NAD oxidoreductase (FAO), β-galactosidase, β-hexosaminidase, biotinidase Buffy coat by electron microscopy inclusions Muscle and nerve biopsy	*POL3A* and *POL3B*, Chromosomal analysis for18q micro-deletion involving *MBP, TREX1, RNASEH2A, RNASEH2B, RNASEH2C* and *SAMHD1, GFAP, LMNB1, ASPA, CYP27A1,EIF2B1-5, FUCA1, GALC, PSAP, FAM126A* (known also as *DRCTNNB1A* or *HCC*), *LHGDG, DARS2, MLC1* and *MLC2, ARSA, PSAP, SUMF1, GJA1, PLP1* and *GJA12*, different *PEX* genes, *GBE1, RNASET2, SLC17A5, HSD17B4, ACOX, SCP2, ALDH3A2, SOX10* Genes for Leukodystrophy mimickers: *ADSL, SLC25A12, AIMP1, OCLN, NOTCH3, HTRA, ERCC6, ERCC8 , XPG, XPB, GTF2H5, TTDN1* and *XPD, COL4A1, MDC1A,POMT1-2, FKTN, FKRP, LARGE, POMGNT, ATN1* for CAG trinucleotide repeats, *QDPR, MANBA, MAN2B, NEU3, ASAH1, FHL1-5, FA2H, FMR1* for CGG trinucleotide repeats, *GALT, GAN, GLB1, HEXA, HEXB* and *GM2A, GPR56, HSPD1, HMGCL, IKBKG, JAM3, MCT8* (*SLC16A2*), *ATP7A, TYMP, SUOX, MOCS1, MOCS2* and *GEPH, MCOLN*, genes for mucopolysaccharidoses, *BTD, HCS, C2orf3, DMPK* for CTG trinucleotide repeats, *CLN1-8, CLC7* or *OSTM, NPC1*and *NPC2, ATP7B, KIAA1840, ZFYVE26, ACP5, OCRL, POLG1* and other genes for mitochondrial depletion, *TREM2* and *DAP12, PDHA1, PDHB, DLAT, DLD, PDX* or *PDP, PC, PHGDH, PSAT* and *PSPH, PTEN*
Part D. Recurrent radiologic testing including MRIs every 6-12 months and CT scans to asses for calcifications	

D4.1.3 NGS testing approaches. Patients will have concomitant WGS based clinical testing at Illumina. Illumina has a dedicated staff with two board certified molecular geneticists and more than seventeen genetic

counselors dedicated to the analysis and interpretation of clinical genomes. Patients and their parents will undergo collection of a blood sample for NGS during the initial clinical visit, after informed consent. NGS approaches will be based on WGS with tired analysis of leukodystrophy associated genes, as defined by those disorders characterized by experts as resulting in leukodystrophies or genetic leukoencephalopathies (see tables 1 and 2 in Appendix F.b), as well as filtered for structural and copy number variations, followed by comprehensive analysis of WGS for novel genes in coding regions only if patients remain unsolved. A NGS timeline will be recorded, including date of sample collection, and start times, completion and reporting for each NGS approach. If a specific known or novel molecular diagnosis is made, the patient will be considered as having achieved the study endpoint, which is a definitive diagnosis. NGS testing will be covered under research budgets to ensure that there is no bias based on available insurance coverage for NGS approaches.

D4.2 Clinical utility data collection

Primary and secondary clinical utility outcomes will be recorded (Schema 3). These will be collected by comparison of patient reports that clinical events occurred and direct weekly contact with the practitioner during a twelve-month period of after diagnosis across all cohorts. Each patient will also consent to the collection of longitudinal natural history information for at least two years after enrollment. This will include medical notes to record changes in care and clinical state, included changes in medical morbidities, surgeries, pharmacologic management of complications and implementation of disease specific therapies.

Financial data collection: Charges will be collected for laboratory testing performed both prior to and as a result of an identified diagnosis. Additionally charges will be collected for practitioner visits both prior to and as a result of diagnostic testing, as well as for additional radiologic, neurophysiologic and functional testing ordered both prior to and as a result of the identified diagnosis.

D4.3 Data analysis: *Sample size and power analyses* are calculated based on the assumption that the proportion of correct diagnosis using the current diagnostic approach is 50 percent (1-3). If we define the proportion of correct diagnosis in the standard (control) arm as p_s and the NGS arm as p_n, then the null hypothesis is H_0: $p_s = p_n$. The alternative hypothesis is H_A: $p_s < p_n$. The total sample size and power for the proportion difference between study arms (d) when equal to 0.20, 0.25, 0.30, 0.35 and 0.40 are demonstrated in Figure 2 and Table 5, assuming each group will have equal sample size and using one-sided Fisher exact distribution. A sample of 200 will provide adequate power of more than 0.85 for differences in proportion of the predicted 0.20 (d=0.20) and will also provide adequate power for establishing differences in time to diagnosis analysis.

Primary outcome measures will be effectiveness, measured by percent success in diagnosis, and duration to diagnosis. Additional primary outcome measures will be changes in disease specific screening or therapeutics. Cox regression analysis will be utilized to evaluate the hypothesis that NGS will shorten the time of diagnosis, or change clinical management.

Missing Data: We will use multiple imputations to account for missing data. Imputation is the substitution of some value for a missing data point. Multiple imputation (MI) is a Monte Carlo technique in which the missing values are replaced by $m > 1$ simulated versions, where m is typically small (between 3-10). [64]

D4.4 Expected Outcomes. We anticipate that NGS, and specifically WGS will result in a greater percentage of definite diagnoses than the current diagnostic approach, with a shorter time to diagnosis. We also anticipate that in some cases NGS approaches will result in a molecular diagnosis where no diagnosis would have been achievable with current diagnostic approaches. We anticipate a substantial increase over current diagnostic effectiveness of 50%, to greater than 70% percent of cases of leukodystrophy using NGS

approaches. We anticipate that some patients will have changes to clinical management, as defined by screening for disease specific complications or implementation of a disease specific therapeutic approach.

Potential Problems and Alternative strategies.

Potential Problem	Solution/ Alternatives
Concerns with randomization in a pragmatic trial design	Careful block randomization will be performed across centers/practitioners, gender, age, and time
Discovery of new leukodystrophy genes	To adequately compare to the current diagnostic approach, NGS approaches will need to be updated to include these novel genes.
Patients who change medical practitioners during the study	Study coordinators will establish direct contact with families and will follow testing and results even if testing occurs outside of the direct study.
Unintended genetic findings with health implications for the parents	For this reason, parental samples will only be used to validate targeted leukodystrophy-related mutations found in their children, and not to look for secondary findings, carrier status or medically important results.
Recruitment of sufficient patients for a rare disorder	The GLIA Centers of Excellence, with an online second opinion program see more than twice the number of patients leukodystrophies are perceived as rare, recent evidence suggests that they are more common than previously recognized [1,65] and we feel confident that we will be able to recruit adequate numbers to make the proposed approaches feasible.

E. Human Subjects (Risks & Benefits)

Subject Characteristics: The heritable leukodystrophies affect males and females equally, with the exception of Pelizaeus Merzbacher and ALD, which are X-linked. We expect therefore that males and females will be equally represented in the population of patients with unclassified leukodystrophies. The age of presentation is variable ranging from infancy to adulthood. All ethnicities are equally represented in these disorders, and we expect ethnicities to be represented based on US census data of population distribution. Projected enrollment is based on patients within the institution with undiagnosed white matter and referral of samples for diagnostic evaluation in the past years. Control subjects will be recruited to be age and sex matched as possible.

Subject Involvement: Patients with suspected leukodystrophy will be provided with information about the study by the PI, a coinvestigator or a collaborating physician (who will provide interested patients with contact information for the PI/study coordinator), and interested participants/or their parents will provide written informed consent. When possible, the PI or a co-investigator will perform a neurologic exam on the participant. If not possible, a copy of the most recent neurologic exam will be requested. In addition, medical records will be requested on all participants, information to be collected includes: all biochemical and genetic studies, neurophysiologic studies, and MRI. Participants will be asked to donate excess samples taken at the time of clinical testing including blood draw, urine samples, lumbar puncture or skin biopsy, or other tissue obtained for clinical or post mortem evaluation. No procedures will be done for the sole purpose of this study, with the exception of a blood draw for DNA extraction or saliva sample collection.

Control Involvement: Control samples will be obtained from several sources (please see table 2 for examples). In the case of banked cerebrospinal fluid or fibroblasts, where no identifying information is associated with the samples, it will not be possible to obtain consent. However, in control subjects undergoing lumbar puncture for a clinically indicated reason, consent will be obtained to use excess cerebrospinal fluid for the purpose of the study. In addition, in the case of excess blood obtained at the time of a clinically indicated venipuncture, individual consent will be obtained.

Protection against risk: Recruitment and Informed Consent:

Study subjects will be referred from a variety of sources including neurologists and geneticists at Children's National Medical Center as well as outside referrals. In all cases the referring physician will contact the PI regarding their patient's potential participation in this study. The physician will be asked to discuss participation in this study with their patient and have their patient contact a genetic counselor or the PI at the PI's institution if they have questions about participation in this study. Subjects interested in

participating in the proposed study will either sign the informed consent when they come to Children's National for clinical evaluation or will be mailed the consent form and conduct the informed consent over the phone with the PI/study coordinator/co-investigator before sending back the signed informed consent. All efforts will be made to minimize any potential risk associated with this study. Risks will include those associated with routine neurological exam and the donation of samples for genetic and proteomic studies, from which the largest risk is that of breaches in confidentiality. In order to maintain confidentiality for all participants, all names will be removed from samples, using only unique identifiers. Identifiers will only be linked to patient names through a password-protected database, accessible only to study personnel. Names are maintained in a database in order to provide patients with clinically relevant information generated from this study. Withdrawal from the study is permitted at any time and would result in removal of any identifying information from recorded databases and destruction of any blood sample, CSF sample, skin culture, or other biologic sample.

F. Inclusion of Women, Children, and Minorities:

Inclusion of women

As leukodystrophies, except for the particular case of Adrenoleukodystrophy and Pelizaeus-Merzbacher disease which are X –linked, equally affect both genders, we expect to enroll an equal number of males and females in the population of patients with unclassified leukodystrophies.

Inclusion of minorities

All ethnic groups are affected by leukodystrophy with little racial predilection. It is expected that the various ethnic groups will be represented in proportional numbers to their populations. If in the course of the study we realize that there is a low representation of minorities, we will make specific efforts to recruit these minority populations.

Inclusion of Children

Children will be primarily studied as most patients affected by leukodystrophies are children.

G. Risks and Side Effects:

Potential risks: Physical risks are those associated with a neurologic evaluation and donation of biologic samples. All samples will be excess samples available after clinically indicated procedures, with the exception of blood samples or saliva samples donated for extraction of DNA. Other risks associated with this study are associated with confidentiality. As all patients participating in this study have already received a diagnosis of leukodystrophy there is little risk of discrimination (legal or social) based on participation in this study. Finally, there is the risk of psychosocial stress by being asked to fill out patient reported outcome and quality of life surveys.

Protection against risk: Recruitment and Informed Consent:

Study subjects will be referred from a variety of sources including neurologists and geneticists at Children's National Medical Center as well as outside referrals. In all cases the referring physician will contact the applicant regarding their patient's potential participation in this study. The physician will be asked to discuss participation in this study with their patient and have their patient contact a genetic counselor in the Research Center for Genetic Medicine if they have questions about participation in this study. Subjects interested in participating in the proposed study will either sign the informed consent when they come to a study site for clinical evaluation or will be mailed the consent form and conduct the informed consent over the phone with the PI/co-PIs/study coordinator before sending back the signed informed consent. All efforts will be made to minimize any potential risk associated with this study. In order to maintain confidentiality for all participants, all names will be removed from samples, using only unique identifiers. A Global Unique Identified (GUID) is used as an identifier for individuals participating in this study. The GUID is an 11 Character string that is generated using an encryption

technology and algorithms licensed by the NCRI from the National Institutes of Health (NIH). The GUID is generated on a secure website that utilized 128-bit Secure Socket Layer (SSL). Of note, this website is not directly linked to GLIA or NeuroBANK. The GUID is generated using an irreversible encryption algorithm – it accepts twelve identifying elements (eg. Last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth etc), and produces a unique random generated character or string, the GUID. No identifying system is stored in the system; it is simply used to generate the GUID. If the same information is entered again at another site for example, the same GUID is returned. Identifiers will only be linked to patient names through a password-protected database, accessible only to site study personnel. Names are maintained in a site-specific database in order to provide patients with clinically relevant information generated from this study. Withdrawal from the study is permitted at any time and would result in removal of any identifying information from recorded databases and destruction of any blood sample, CSF sample or skin culture.

H. Benefits:

Potential Benefits of Proposed Research to Subject and Others:

This study is no greater than minimal risk with no intended direct benefit. There is a potential for indirect benefit in developing better diagnosis, further understanding of pathogenesis and outcome markers for clinical trials. We believe that this study will result in new pathophysiologic understanding of these complex disorders, new biomarkers for difficult to diagnose entities and documentation of novel disorders. We feel that although there is no intended direct benefit, there is potential for significant indirect benefit. In addition, as the project evolves and clinically relevant biomarkers for specific disorders are established, validated, and published, clinically relevant results will be reported to the treating physician. These results will be reported via letter, with an explanation of the nature of tests performed on a research basis.

I. Costs To Subjects:

Participants will be responsible for the cost of traveling to Washington, DC; however up to $400 will be available to participants to help defer this cost. Reimbursement for travel costs (up to $400) will be provided with receipts. Every effort will be made to help participants arrange flights through the National Patient Travel Center (charitable flights for medically related travel). There will be no cost to the patient for the clinical evaluation or any of the tests specifically indicated in this research protocol. Any clinically indicated tests will be billed to the patient's insurance.

J. Conflicts Of Interest:

The investigators have no conflict of interest.

K. Facilities and Equipment

Laboratory:

Dr. Hoffman's laboratory is located at the Research Center for Genetic Medicine. The whole center occupies 10,000 square feet of laboratory space (free space) on the 5th floor of the Children's National Medical Center (Children's National), Children's Research Institute (CRI). Core laboratory research equipment (ultra-low freezers, centrifuges, liquid nitrogen tanks) are housed in 5,000 sq. feet of space shared by all investigators.

Computer: Desktop computers are available to the PI for use. The Research Center for Genetic Medicine employs a full-time computer administrator, a full-time Oracle database administrator, a full-time web-master, and a full-time hardware/software technician to maintain an independent computer network with its own dedicated T1 lines. The network is flexible, adaptable, and heterogeneous,

consisting of various makes and models of computers. The main servers are Compaq Proliant 800 and two 3000 models with single 450 MHz and dual 400 MHz processors, respectively. These servers are connected via a Cisco Pix firewall through a Cisco router to a dedicated T1 connection to UUNet, a global leader in the internet backbone. The network runs Windows NT 4.0 on both servers and workstations and supports other operating systems, i.e., Windows 95, 98, Macintosh, and the necessary connections to the Novell Netware and applications located on the Children's National's computer network. Connection between the servers and the workstations located on the research floor is via a fiber-optic link through Cisco Catalyst 4000 Gigabit Ethernet ports and Cisco Catalyst 3548 switches resulting in a minimum of 2 gigabyte full duplex throughput. The main e-mail system consists of an Exchange 5.5 Server and Outlook 2000 with web access. The servers are configured with RAID 5 configuration and utilize both DAT and DLT tape backups running Veritas Backup Exec for reliability, security, and dependability. Other servers on the network include: 1) a Macintosh G4 with dual 500 MHz processor for the Apple "branch" of the CRI network domain, 2) a Micron NP3400 server with dual 750 MHz processors acting in the Web Server role, located in a "DMZ" of the Pix firewall for security and currently hosting 7 separate websites, 3) a Hewlett-Packard NetServer as a Print/Fax Server, 4) a dedicated server for the Trend Micro Antivirus monitoring, update, and deployment of the latest antivirus protection for workstations, servers and email systems, 5) a Sun Microsystems Enterprise Vectra 450 for complex mathematical computations, and 6) a Compaq ML 570 with 4 Xenon 700 MHz processors configured as an Oracle database, server. The workstations consist of Compaq EN Pros, Micron Millenia mini-towers, Apple G-3's and G-4's and Dell GX1 and GX110 desktops, along with laptops that provide mobility for the researcher. The Affymetrix LIMS database, run within the Oracle environment, interfaces with the web to provide public access to these files. Software licenses held by the Research Center for Genetic Medicine include for gene array analysis and temporal profiling (GeneSpring®, Affymetrix Microarray Suite® and Data Mining Tool®, GenePix®); and for digital imaging and graphics capabilities (Adobe Photoshop® 6.0, Image Pro® Plus, and UnScanIt®).

Office: The PI has available office space in the Center for Genetic Medicine and the Department of Neurology at Children's National.

Major equipment: The PI has full access to all the shared facilities at the Research Center for Genetic Medicine houses four Affymetrix GeneChips® stations, including 4 GeneChip® Fluidics Station, 4 GeneArray® scanners, and 2 GeneChip® hybridization ovens. Affymetrix data resides in an Oracle LIMS system. In addition we have an Axon GenePix4000 cDNA array dual channel scanner and a Gene Machine robotic arrayer with 16 printing pins and a 36 plate robotic plate feeder for the arrayer. The Research Center houses a Biomek FX robot, two ABI3700 96 capillary sequencers, two ABI3100 16 capillary sequencers, one ABI377 slab sequencer, five 96-well MJ tetrad PCR machines (20 blocks total), and eight Perkin-Elmer 9600 PCR machines. In addition, the Center has two 8-capillary automated sequencers (Beckman CEQ2000), two LiCor infrared gel-based automated sequencers, two ABI 3100 capillary-based automated sequencers, and four single 96-well block MJ PCR machines. Further equipment includes a Beckman XL-90UC ultracentrifuge, Savant speedvac plus, Brinkman polytrons, Hitachi GeneSpec III spectrophotometers, Arcturns Laser Capture Microscope, Nikon Microphot FXT microscope with fluorescent filter blocks and Optonics PE750 digital camera, cryostat, and Licor infrared imager for western blots. The Center has also recently purchased an ABI 4700 Proteomics TOF/TOF unit with a MDLC front end. All other equipment and software for modern molecular biology, immunocytochemistry, immunoblotting, histopathology, and tissue culture are housed within the Research Center for Genetic Medicine.

L. References & Literature Cited

Please see endnotes for references.

M. List of Appendices

Please see attached for all applicable forms.

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F. Appendix F: Relevant Publications
    a. F.a: The Symptomatic Management of Leukodystrophy Patients
    b. F.b: Case definition and classification of leukodystrophies and leukoencephalopathies

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Disease Activity Rating Scale				
Symptom	**Rating (Circle one)**			
Crying	0	1	2	3
0= no crying 2 = inconsolable >2 minutes OR cry intermittently for <10 minutes 3 = inconsolable >2 minutes AND cry intermittently for >10 minutes				
Length of Uninterrupted Sleep	0	1	2	3
0 = sleeps more than 3 hours for infants< less than 6 months; more than 6 hours for children over 6 months 1 = sleeps 2–3 hours at a time for infants less than 6 months; more than 4-5 hours for children over 6 months 2 = sleeps 1–2 hours for infants less than 6 months,; more than 2-3 hours for children over 6 months 3 = sleeps <1 hour for infants less than 6 months; greater than 1-2 hours for children over 6 months				
Generalized seizure	0		8	
0 = no seizures 8 = tonic-clonic, subtle staring, chewing, arching				
Fever	0		1	
0 = No fever 1 = temp greater than or equal to 37.3°C (99.1°F)				
Excessive Irritability	0	1	2	3
1 = consoling calms infant in 3–5 minutes 2 = consoling calms infant in 6–15 minutes 3 = consoling calms in >15 minutes or not at all				
Skin Findings body	0	1	2	3
0= no rashes 1= blotchy red rash which comes and goes 2=persistently red spots which stay 3= persistent spots which do not blanche when pressed on				
Skin Findings hands, feet and ears	0	1	2	3
0= no rashes 1= blotchy red rash which comes and goes 2=persistently red spots which stay 3= persistent spots which do not blanche when pressed on				