Title:	**Janus Kinase Inhibitor (Baricitinib) for Aicardi Goutières Syndrome**
Short Title	JAK inhibitor treatment in AGS
Drug or Device Name(s):	Baricitinib
FDA IND	140510
Regulatory Sponsor:	Adeline Vanderver, MD
eIRB Number	18-015414
Protocol Date:	11 April 2019

Amendment 1: 23 Jun 2020 (Full Amd.)	Amendment 9: 17 Sep 2020 (Full Amd.)
Amendment 12: 13 Jul 2021 (Full Amd.)	Amendment 19: 29 Jul 2021 (Full Amd.)
Amendment 22: 12 Jan 2022 (Full Amd.)	Amendment 24: 18 Mar 2022 (Full Amd.)
Amendment 28: 19 August 2022 (Full Amd.)	Amendment 32: 02 May 2023 (Full Amd.)
Amendment 36: 30 Oct 2023 (Full Amd.)	Amendment 44: 05 Feb 2025 (Full Amd.)

Please note that the above list does not include 'Staff Change' amendments.

IND holder
Adeline Vanderver, MD
Program Director of the Leukodystrophy Center of Excellence
Children's Hospital of Philadelphia
Associate Professor of Neurology
3615 Civic Center Blvd.
Abramson Research Center 516H
Philadelphia, PA 19104
Phone: 215-590-1719
Fax:215-590-1234
Email: vandervera@chop.edu

Study Principal Investigator
Adeline Vanderver, MD
Program Director of the Leukodystrophy Center of Excellence
Children's Hospital of Philadelphia
Associate Professor of Neurology
3615 Civic Center Blvd.
Abramson Research Center 516H

Philadelphia, PA 19104
Phone: 215-590-1719
Fax:215-590-1234
Email: vandervera@chop.edu

Study Biostatistician:
Justine Shults, PhD
Children's Hospital of Philadelphia
Professor of Biostatistics
4471 Roberts Center for Pediatric Research
624R Schuylkill Ave
Philadelphia, PA 19146
Phone: 215-518-8628
Fax: 215-590-1234
Email: shultsj@chop.edu

Medical Monitor:
Nicole Jaffe, MD
Clinical Assistant Professor of Pediatrics
Complex Care Pediatrics
Children's Hospital of Philadelphia
34th and Civic Center Blvd
Philadelphia, PA 19104
Email: jaffen@chop.edu

Co-investigators:

Laura Adang, MD PhD
Instructor, Department of Neurology
Children's Hospital of Philadelphia
34th and Civic Center Blvd
Philadelphia, PA 19104
Email: adangl@chop.edu

Amy Waldman, MD
Assistant Professor, Department of Neurology
Children's Hospital of Philadelphia
34th and Civic Center Blvd
Philadelphia, PA 19104
Email: waldman@chop.edu

Please refer to FDA form 1572 and the eIRB application for an exhaustive list of co-investigators and other study team members.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS OF TERMS

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.
AGS	Aicardi Goutières Syndrome
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).
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CSF	Cerebrospinal fluid
CXR	Chest X-ray
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
GEE	Generalized estimating equation
GMFM-88	Gross Motor Function Measure-88
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
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
ISG	Interferon stimulating genes
IV	Intravenous
IVIg	Intravenous immune globulin
JAK	Janus kinase
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.
MDBP	Myelin Disorders Biorepository Project
Patient	A study participant who has the disease or condition for which the investigational product is targeted.
PH	Pulmonary hypertension
PK	Pharmacokinetic
PPD	Purified protein derivative
QD	Once daily
QLS	Quasi-Least Squares
RA	Rheumatoid arthritis
SAE	Serious adverse event

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.
SLE	Systemic lupus erythematosus
STAT	Signal transducers and activators of transcription
STING	Stimulator of interferon genes
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
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
WBC	White blood cell

ABSTRACT

Context: (Background)
Aicardi Goutières Syndrome (AGS) is a multisystem, heritable disorder of innate immunity resulting in excessive interferon production. Interferon production causes injury to the brain, as well as the skin, liver, lungs, heart and many other organs. Treatment with Janus Kinase (JAK) inhibitors offers the promise of decreasing interferon signaling and limiting the morbidity of this devastating disorder.

Objectives: (Primary and important secondary objectives)
The primary objective is to assess safety as well as efficacy of baricitinib, a JAK inhibitor, in patients with Aicardi Goutières Syndrome. Efficacy will be determined primarily by changes in the AGS scale from baseline to 52 weeks of treatment.
The secondary objectives include assessments of safety parameters, of therapeutic endpoints including an AGS symptom diary score; a surrogate biomarker, the interferon signaling gene score; and of functional neurologic measures (including GMFM-88 and longitudinal AGS scale measurements [in addition to and including baseline and 52 weeks]).

Study Design:
Open-label phase 2 clinical study.

Setting/Participants:
The setting: outpatient
The number of sites: single center
The number and description of participants including key eligibility criteria: eligible patients will have AGS with symptoms of neurologic disability, laboratory evidence of AGS related disease, or skin involvement, and no exclusion criteria making the administration of baricitinib less safe.
Clinical care and research procedures will be used to generate data about the use of baricitinib in patients affected by AGS, which may potentially help to improve treatment outcomes for subjects within this patient population.

Study Interventions and Measures:
The research procedures include physical examination, vital signs, symptom diaries (for at least two years from treatment initiation), medical record review, functional neurologic measures such as the GMFM-88 assessment or the AGS scale, assessment of skin inflammation, laboratory evaluations and phlebotomy including PK testing and leftover samples for future research, interferon signaling scores, pregnancy testing, and administration of baricitinib. Throughout the protocol, note that the term “study interventions” includes clinical and research procedures used to generate study data.
Main study outcome measures include the AGS scale, symptom diaries, safety monitoring, functional assessments of neurologic function (ie GMFM-88), and interferon signaling gene scores.

PROTOCOL SYNOPSIS

Name of Investigational Product:	Baricitinib, orally or G-tube administered
Title of Study:	Janus Kinase Inhibitor (Baricitinib) for Aicardi Goutières Syndrome
Length of Study:	Each patient may be treated up to 288 weeks.
Number of Planned Patients/Subjects:	Entered: up to 55 Enrolled: up to 55 Completed: up to 55
Study Objective:	To assess safety and efficacy of baricitinib in individuals affected by Aicardi Goutières Syndrome
Study Population and Main Eligibility/ Exclusion Criteria:	Individuals with Aicardi Goutières Syndrome with evidence of AGS related neurologic or systemic disease and without systemic medical problems placing them at higher risk for treatment with baricitinib.
Primary Outcome Measures:	The primary objective is to determine if the administration of baricitinib to patients with AGS results in an improvement or stability of the AGS scale from baseline to 52 weeks.
Secondary Outcome Measures:	Secondary objectives will include assessments of safety parameters, improvement of interferon signaling scores, improvement of AGS scale (longitudinal) and GMFM-88, and improvement of a daily disease severity scale, for the duration of the treatment period.

Study Design:	Open- label, phase 2 clinical study.
Statistical Considerations (sample size and analysis plan):	The change over time in AGS scale will be compared pre and post treatment with a GEE analysis that accounts for age at treatment initiation. Sensitivity analyses will also be performed, to evaluate the efficacy of treatment across several statistical approaches with varying assumptions. Sample size considerations were based on preliminary data. In preliminary data, the average of within subject changes (post-treatment average minus pre-treatment average) was 0.80 with a standard deviation of changes of 1.04. This corresponds to an effect-size of 0.80/1.04 = 0.77. From PASS 16, a sample size of 30 data pairs achieves 98.3% power to reject the null hypothesis of zero effect size when the population effect size is 0.77 and the significance level (alpha) is 0.050 using a two-sided paired t-test. Should the effect-size be smaller than we observed in our preliminary data, we will have 80% power to detect an effect size of 0.53, which corresponds to an average of within subject changes of 0.55, if the SD of changes is 1.04.
Funding Sponsors (federal, state, foundation and industry support):	Drug and grant support provided as a donation by Eli-Lilly Secondary funder: Pennsylvania Department of Health

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

The purpose of this immediate and delayed phase study protocol is to establish safety and efficacy of baricitinib in individuals with **Aicardi Goutières Syndrome (AGS),** a heritable disorder of excessive interferon (IFN) production**,** occurring in fewer than 1/7000 live births[1], that affects brain, skin, bone marrow and visceral organs**.** This rare condition is well positioned for new therapeutic innovations due to growing interest in targeting interferon pathways also implicated in more common disorders such as lupus and rheumatoid arthritis. In addition, AGS is increasingly well characterized, with an established course of disease[2], improved early recognition through laboratory criteria[3,4] , MRI[2,5], and well characterized genotyping[6-9]. Genetic abnormalities in viral sensing genes (*TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, IFIH1*[6-9]) trigger an endogenous IFN response resulting in extensive end organ damage. (**Figure 1**). IFNs, increased in blood and cerebrospinal fluid in AGS[10,11], are thought to be directly responsible for disease pathology. Transgenic animal models of IFN overexpression in astrocytes demonstrate a thrombotic microangiopathy[12], similar to pathology seen in AGS brain and skin lesions[13-15]. There is evidence of vascular injury in vitro in vascular endothelial cells exposed to IFN[14] and in humans treated with recombinant IFN[16], suggesting tissue specific injury. New data suggests that treatment with **IFN blockade using Janus Kinase (JAK) inhibitors** may be beneficial in interferon mediated disorders. Since opening our **expanded access use program for baricitinib, a JAK inhibitor, in February 2017, we have enrolled more than twenty individuals**. Preliminary data[17,18] suggests improvement in patient reported scores and expression of IFN signaling genes, however, more comprehensive and longer-term study is needed to assess clinical benefit of this therapeutic approach.

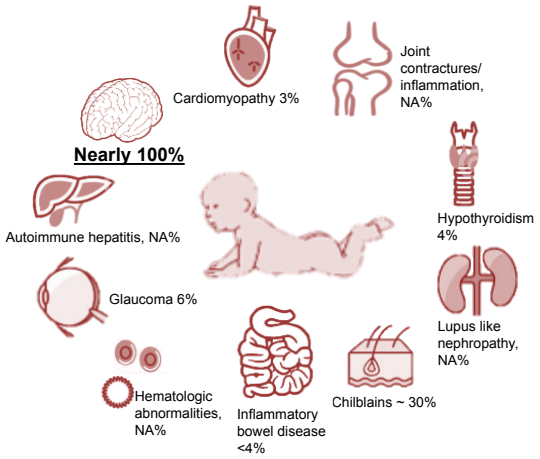


Figure 1. Multisystemic effects of AGS-related interferon include primary neurologic involvement including leukodystrophy with a calcifying thrombotic microangiopathy, microcephaly, seizures and severe developmental delay.

Aicardi-Goutières Syndrome (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, pulmonary hypertension, myopathy, neuropathy, endocrinologic problems) in many patients. All available literature sources suggest that the prevalence of AGS is well below 5 in 10,000 persons.

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 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.

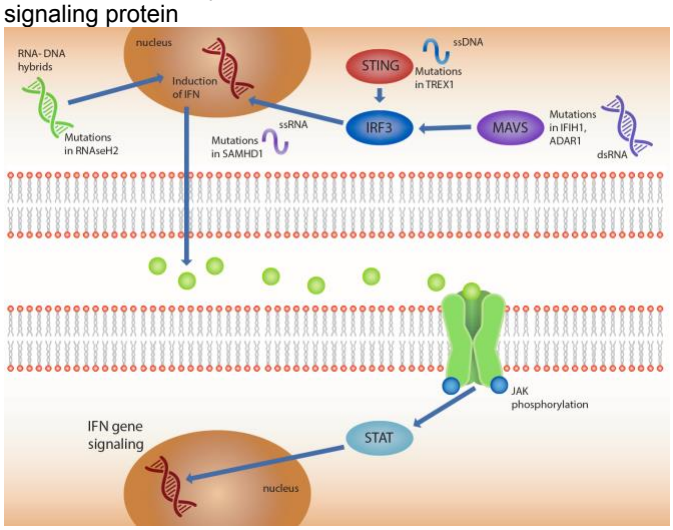
AGS is associated with increased levels of interferon alpha in the cerebrospinal fluid (CSF) and serum. However, interferon alpha levels, and white cell counts, in the CSF have been reported to fall over the first few years of life, perhaps corresponding with an apparent clinical "burning-out" of the 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 most 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.

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. Additional phenotypes are now being identified and include later onset disease after a year of age.[19] 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[20].

Thus, although a minority of 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[19]. 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.

Figure 2. Janus Kinase and IFN pathways. ssDNA- single stranded DNA, ssRNA- single stranded RNA, dsRNA- double stranded RNA, STING- stimulator of IFN genes, STAT- signal tranducers and activators of transcription, IRF3- Interferon regulatory factor 3, MAVS- Mitochondrial antiviral-signaling protein



1.2 Name and Description of Investigational Product or Intervention

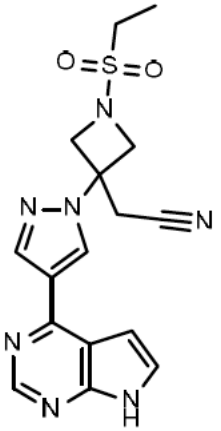
Description of baricitinib, a JAK inhibitor and rationale for treatment

The **Janus Kinases (JAKs)** are the principal family of kinases associated with signal transducers and activators of transcription (STAT) phosphorylation and activation[21]. 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 and psoriasis[22,23]. JAK/ STAT pathway [21,24,25] inhibitors block downstream effects of IFN, preventing signaling after IFN receptor activation. **Baricitinib is an orally administered JAK1/2 inhibitor** which affects IFN type I receptors implicated in AGS. Since opening our **expanded access use program for baricitinib, a JAK inhibitor (NCT01724580- hereafter referred to as JAGA), in**

February 2017, we have enrolled over twenty individuals. Preliminary data suggests improvement in patient reported scores and expression of IFN signaling genes.

Baricitinib Nomenclature
International Nonproprietary Name (INN): baricitinib
Chemical Abstracts Service (CAS) Number: 1187594-09-7
Lilly compound number: LY3009104
Chemical name (International Union of Pure and Applied Chemistry [IUPAC]):
2-(3-(4-(7H-pyrrolo[2,3-d] pyrimidin-4-yl)-1H-pyrazol-1-yl)-1-(ethylsulfonyl) azetidin-3-yl) acetonitrile
United States Adopted Names (USAN): baricitinib

Chemical Structure



1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Non-Clinical Studies

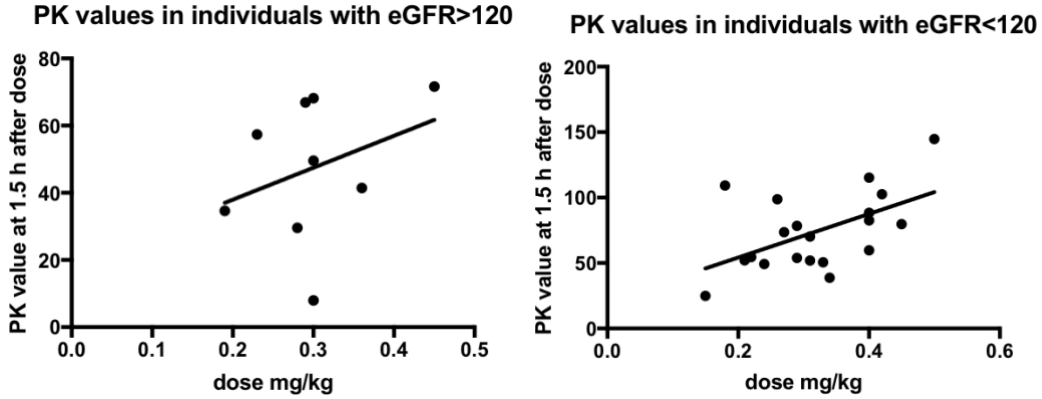
Please see the prescribing information for pre-clinical studies.

1.3.2 Clinical Studies

1.3.2.1 Human Pharmacokinetics

PK values for dosing tables (**Appendices 3 and 4**) were generated from experience using baricitinib in adults as well as children with other genetic interferonopathies[26]. Additionally, preliminary data in our patient cohort demonstrated that PK values for AGS affected individuals with eGFR <120 were between 50-100 ng/ml for doses of 0.2-0.4 mg/kg/day and for individuals with eGFR ≥120 were between 40-60 ng/ml for doses of 0.2-0.4 mg/kg/day. The observed Cmax (roughly at 60-90 minutes post dose) at stable dose in these individuals is ~70 ng/mL. This corresponds to pediatric data in patients with other genetic interferon disorders studied at the National Institutes of Health, in whom at stable dose for the few patients with eGFR<120 ranged from 60-80 ng/mL, and for patients with eGFR ≥120 ranged from 50-70 ng/mL (communication from Eli Lilly).

Figure 3: PK values in children with AGS treated with baricitinib. Measurements at 1.5 hours post dose



1.3.2.2 Clinical Studies in Adults

Safety of Baricitinib in general clinical studies

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. Extended safety of baricitinib from all patients exposed to any baricitinib dose (including non-approved doses) pooled from 9 clinical trials (one completed phase 1, three completed phase 2, four completed phase 3 and data through April 1, 2017, from one ongoing phase 3 long-term extension study).

As of 13 August 2022, a total of 14,233 patients received baricitinib in clinical studies. Baricitinib has been approved for clinical use in adult patients in both the European Union and the United States.

- The most commonly reported treatment-emergent adverse events (TEAEs) in patients with RA are upper respiratory infections, nausea, herpes zimplex, and herpes zoster.

- The most commonly reported TEAEs in patients with COVID-19 are increases of liver enzymes, thrombocytosis, creatine phosphokinase increases, neutropenia, deep vein thrombosis, pulmonary embolism, and urinary tract infection.
- The most common alterations in laboratory values involve neutropenia, platelet elevations, liver enzyme elevations, lipid elevations, and creatine phosphokinase elevations.
- Some patients also had decreases in hemoglobin and white blood cells ([WBCs]; neutrophils and other white cell lines).
- Adverse events of special interest include serious infections (including tuberculosus and opportunistic infections), malignancy, and thrombosis. The most common serious infections were pneumonia, herpes zoster, and urinary tract infections.
- As part of the extended safety analysis, 3 individuals were noted to have a gastrointestinal perforation.
- More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) may be found in the Prescribing Information. Information on AEs expected to be related to the investigational product may be found in Section 6 (Adverse Reactions) of the Prescribing Information.

1.3.2.3 Clinical Studies in Children

Safety of Baricitinib in AGS pediatric patients and dosing rationale.
Overall, baricitinib was well tolerated by the AGS population. Over the duration of collected data, there were 49 hospitalizations in 22 subjects, all attributable to AGS and complications related to severe neurologic disease. This included urinary tract infections, seizures, admission for viral syndromes with respiratory distress or dehydration, pneumonia-including aspiration pneumonia, erythema multiforme, fracture, acute neurologic change, and planned interventions. One patient died during the enrollment phase, prior to drug initiation, from AGS-related complications. On study, one individual died secondary to pulmonary hypertension related to AGS while on study at day 428[27]. A second individual died after the data lock, while on study at day 1357. This death occurred in the context of a multisystem illness resulting in worsening pretreatment chronic liver failure with ascites and hypogammaglobulinemia, worsening of pretreatment pulmonary hypertension, leukopenia, anemia, worsening pretreatment thrombocytopenia requiring chronic steroids, and renal insufficiency. Autopsy revealed a fungal pneumonia, which had not been detected on pre-mortem cultures, and was possibly attributable to the study medication.
Throughout the trial, dose adjustments were based on changes in weight, pharmacokinetic data, baseline eGFR and re-emergence of symptoms, according to the study protocol[7,11]. In most children, dose was stable or increased during the study. However, the medication was additionally decreased in several cases due to changes in laboratory parameters. In 4 children, drug dosage was decreased during the study period for BK viremia (n=1), thrombocytosis (n=2), anemia (n=1).
Many individuals began the study with abnormal laboratory values (**Table 1A**). We used odds-ratios to compare the odds of having specific laboratory abnormalities on study versus at baseline (available data prior to drug) (**Figure 4**). After starting study

medication, markers of liver dysfunction were transiently abnormal in a subset of subjects (ALT abnormal in n=10/35; AST n=20/35; GGT n=30/35), but overall improved on therapy (**Table 1B**). ALT decreased overall in treated subjects [estimated odds-ratio = .3 (95% CI = 0.2 to 0.5, Wilcoxon signed-rank test p = <0.005)]. After treatment, a decreased number of subjects met grade 3-4 severity criteria for GGT (n=4), ALT (n=1) and AST (n=1) abnormalities without statistical significance (**Figure 4, Table 1B**).

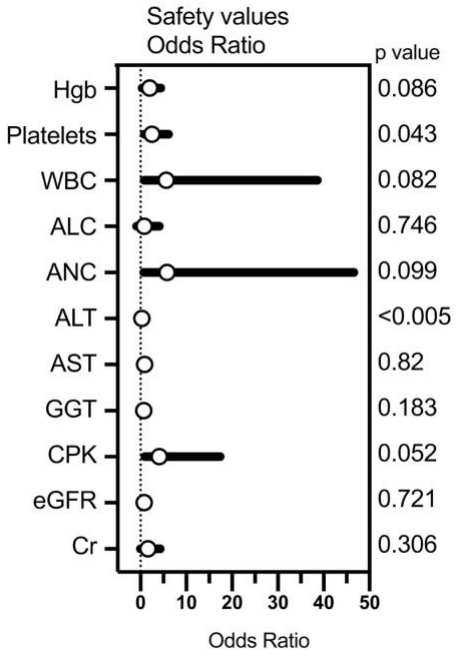


Figure 4. Odds-ratio calculations for safety parameters, comparing safety grades (abnormal versus normal) on study versus before study. Presented as Odds-Ratio with 95th percentile confidence interval; p-value for the Wald's test that the coefficient for on study is zero.

Nineteen individuals had a grade 1-2 or greater anemia [estimated odds-ratio = 2 (95% CI 0.9-4.4, Wilcoxon signed-rank test p=0.086)] (**Figure 4**). One individual had a history of iron-infusion dependent anemia and required this therapy for grade 3 anemia (hemoglobin <8.0 g/dL) in the second year of treatment, at which point the dose was decreased. This was same individual who later died from infection.

The majority (n=20/35) of subjects were found to have platelet abnormalities on study. The majority of these abnormalities represented an increase in platelet numbers, all grade 1-2 [estimated odds-ratio = 2.5 (95% CI = 1 to 6.1, Wilcoxon signed-rank test p = 0.043)] which resulted in decreased dosing in two individuals (**Figure 4**). Four individuals had Absolute Neutrophil Counts (ANC) that were transiently between 500-1000 cells/ul [estimated odds-ratio = 5.8 (95% CI = 0.7 to 46.6, Wilcoxon signed-rank test p = 0.099)] (**Figure 4**). No individuals had decreases of the Absolute Lymphocyte Counts (ALC) <500 during the reporting period [estimated odds-ratio = 0.8 (95% CI 0.1-4.1, Wilcoxon signed-rank test p=0.746)] (**Figure 4**).

Two individuals had reversible elevations of alkaline phosphatase after treatment, which were investigated and found to be consistent with transient hyperphosphatasemia of childhood, a common finding in this age group with no clinical significance. Two individuals had transiently elevated creatinine kinase. In general, creatinine and estimated glomerular filtration rates (eGFR) were stable during the study period and did not require dose adjustments after starting intervention.

Five children received systemic steroids at prior to the study initiation for symptom management (n=3 for skin, n=1 for neurologic dysfunction, n=1 for thrombocytopenia), and these were decreased (n=2) or discontinued (n=3) by their local teams while on study.

Table 1. Safety Measures

A. Maximum laboratory abnormalities prior to study

Grade	0	1	2	3	4	Total
Laboratory parameter	N (%)	N (%)	N (%)	N (%)	N (%)	N
ABSOLUTE LYMPHOCYTES	32 (94.1)	2 (5.9)	0 (0)	0 (0)	0 (0)	34
ABSOLUTE NEUTROPHILS	31(96.9)	1 (3.1)	0 (0)	0 (0)	0 (0)	32
LEUKOCYTOSIS	32 (100)	0 (0)	0 (0)	0 (0)	0 (0)	32
LEUKOPENIA	32 (91.4)	3 (8.6)	0 (0)	0 (0)	0 (0)	35
THROMBOCYTOSIS	30 (96.8)	1 (3.2)	0 (0)	0 (0)	0 (0)	31
THROMBOCYTOPENIA	30 (88.2)	3 (8.8)	1 (2.9)	0 (0)	0 (0)	34
ALANINE AMINOTRANSAMINASE (ALT/SGPT)	18 (51.4)	15 (42.9)	1 (2.9)	1 (2.9)	0 (0)	35
ALKALINE PHOSPHATASE (AP)	34 (100)	0 (0)	0 (0)	0 (0)	0 (0)	34
ASPARTATE AMINOTRANSAMINASE (AST/SGOT)	14 (40)	20 (57.1)	1 (2.9)	0 (0)	0 (0)	35
CHOLESTEROL	31 (88.6)	3 (8.6)	1 (2.9)	0 (0)	0 (0)	35
CPK	32 (94.1)	3 (5.9)	0 (0)	0 (0)	0 (0)	34
CREATININE	24 (68.6)	11 (31.4)	0 (0)	0 (0)	0 (0)	35
GAMMA GLUTAMYL TRANSFERASE	14 (40)	12 (34.3)	6 (17.1)	3 (8.6)	0 (0)	35
HEMOGLOBIN	29 (82.9)	6 (17.1)	0 (0)	0 (0)	0 (0)	35
RETICULOCYTE COUNT	16 (47.1)	18 (52.9)	0 (0)	0 (0)	0 (0)	34
TRIGLYCERIDES	25 (71.4)	9 (25.7)	1 (2.9)	0 (0)	0 (0)	35
eGFR	29 (82.9)	6 (17.1)	0 (0)	0 (0)	0 (0)	35
Total	**391 (75.5)**	**112 (21.6)**	**11 (2.1)**	**4 (0.8)**	**0 (0)**	**518**

B. Maximum laboratory abnormalities on study

Grade	0	1	2	3	4	Total
Laboratory parameter	N (%)	N (%)	N (%)	N (%)	N (%)	N
ABSOLUTE LYMPHOCYTES	27 (77.1)	8 (22.9)	0 (0)	0 (0)	0 (0)	35
ABSOLUTE NEUTROPHILS	14 (40.0)	16 (45.7)	5 (14.3)	0 (0)	0 (0)	35
LEUKOCYTOSIS	35 (100)	0 (0)	0 (0)	0 (0)	0 (0)	35
LEUKOPENIA	20 (57.1)	11 (31.4)	4 (11.4)	0 (0)	0 (0)	35
THROMBOCYTOSIS	15 (44.1)	15 (44.1)	3 (8.8)	1 (2.9)	0 (0)	34
THROMBOCYTOPENIA	30 (88.2)	3 (8.8)	1 (2.9)	0 (0)	0 (0)	34
ALANINE AMINOTRANSAMINASE (ALT/SGPT)	13 (37.1)	21 (60)	0 (0)	0 (0)	1 (2.9)	35
ALKALINE PHOSPHATASE (AP)	27 (77.1)	6 (17.1)	0 (0)	2 (5.7)	0 (0)	35

ASPARTATE AMINOTRANSAMINASE (AST/SGOT)	0	30 (85.7)	4 (11.4)	1 (2.9)	0 (0)	35
CHOLESTEROL	21 (60)	13 (37.1)	0 (0)	0 (0)	1 (2.9)	35
CPK	18 (51.4)	12 (34.3)	4 (11.4)	1 (2.9)	0 (0)	35
CREATININE	13 (37.1)	22 (62.9)	0 (0)	0 (0)	0 (0)	35
GAMMA GLUTAMYL TRANSFERASE	5 (14.3)	20 (57.1)	6 (17.1)	4 (11.4)	0 (0)	35
HEMOGLOBIN	15 (42.9)	13 (37.1)	6 (17.1)	1 (2.9)	0 (0)	35
RETICULOCYTE COUNT	3 (8.6)	32 (91.4)	0 (0)	0 (0)	0 (0)	35
TRIGLYCERIDES	17 (48.6)	13 (37.1)	5 (14.3)	0 (0)	0 (0)	35
eGFR	19 (54.3)	16 (45.7)	0 (0)	0 (0)	0 (0)	35
Total	**226 (43)**	**249 (47.4)**	**38 (7.2)**	**10 (1.9)**	**2 (0.4)**	**525**

Additional Safety Monitoring- Cardiac and Pulmonary Hypertension Monitoring

Pulmonary hypertension (PH) is a rare but potentially fatal disorder characterized by severe vasculopathy and elevated pulmonary artery pressures leading to right-sided heart failure. Progressive PH has both genetic and inflammatory influences [28-34]. In particular, type I interferons, as are overexpressed in AGS, have been established as risk factors for the development of PH [29,35-38]. We have identified several individuals within our cohort with PH, as related to systemic interferon overexpression[27]. Cardiac involvement will be quantified using clinical assessment and echocardiogram. Individuals affected by AGS will have clinical cardiac evaluations every other year, with additional management as clinically indicated. In the patients identified as being affected by PH, we will follow the relationship between PH and the response to baricitinib.

1.4 Selection of Drugs and Dosages

Dosing formulations in use in this study will be limited to the 1 and 2mg tablets and will be used without splitting. Dispersion will be permitted to aid in administration based on IND data submitted to the FDA by Eli Lilly with a letter of cross-reference and according to recently updated product information. Administration is also allowed via clinically placed gastrostomy feeding tube (G-tube) or nasogastric tube, as well as via oral dispersion for patients who are unable to swallow whole tablets. Guidance for alternative administration for participants unable to swallow whole tablets is available in the Olumiant package insert.

As the FDA-approved dose in adults with rheumatoid arthritis is 2 mg each day, the rationale for the starting dose in the AGS subjects and dose modification guidelines are detailed in protocol Section 4.3.

Dosing tables will be based on PK studies conducted by Eli-Lilly and are provided in Appendices 3 and 4.

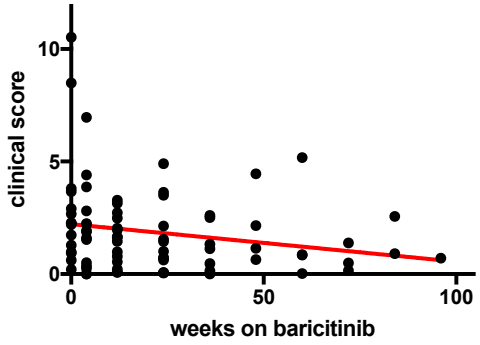
1.5 Relevant Literature and Data

AGS is a monogenic disorder resulting from loss-of-function (except in the case of IFIH1) mutations in any of several distinct genes, resulting in a type 1 interferonopathy associated with both peripheral manifestations and devastating neurologic consequences. 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 clinical trial is to establish whether baricitinib can be effectively used to treat children affected by AGS.

Measurement of Clinical Diary Scores

As interferon levels can fluctuate daily in individuals affected by AGS, we have established a daily self-measure of systemic inflammation, the daily AGS symptom diary (Figure 5 and Appendices 5 and 6). This clinical diary has been in use in the Lilly-sponsored expanded access program for the JAK inhibitor baricitinib (**NCT01724580, JAGA**) since February 2017. As part of the protocol, each patient or patient-proxy completes a daily assessment of symptomatology. This includes a minimum of 2 weeks of baseline daily scores, daily reports while on study drug, and in the case of drug cessation, an additional 28 days of diary entries. Two forms of the diary are offered: paper and electronic, as administered through REDCap. The diary allows for daily assessment of systemic signs of inflammation, and includes family-based assessment of irritability, skin findings, and hyperthermia (Appendices 5 and 6). The clinical diaries have shown to be responsive to baricitinib (Figure 5). The diary scores will be further validated against other outcome measures, as described below.

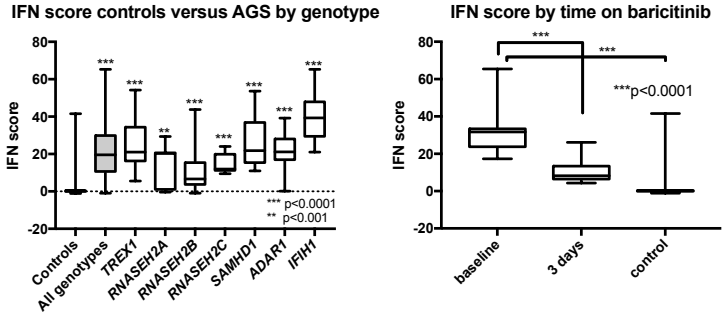
Figure 5: Clinical symptom diary score in AGS affected individuals and improvement on treatment.



Measurement of IFN signaling gene scores

IFN scores are based on mRNA expression of IFN signaling genes (ISG) and represent a surrogate marker for autoinflammation in a variety of disorders [39-41]. IFN scores based on mRNA expression of ISGs have been used to assign a severity score of autoinflammation in a variety of disorders, including AGS [4] and systemic lupus erythematous [39,40]. We measured ISG in individuals affected by AGS as per established protocol [4,42,43]. ISG

Figure 6: **ISG based IFN score**. In left panel, elevated IFN signaling gene scores (ISG) in AGS (n= 180 samples) and controls (n=104), with significant increases across all AGS genotypes. In right panel, response of this score to treatment with baricitinib (in 12 affected individuals with paired results at baseline and at 4 hours post dose 72 hours after drug initiation). Although ISG scores do not normalize, they are decreased from pre-treatment scores (Mann-Whitney, p<0.001). Based on existing data in our laboratory, this approach has a sensitivity of 89.86% (95% CI 83.83-94.22) and specificity of 82.61% (95% CI 73.30-89.72).



scores were calculated for all AGS affected individuals in the MDBP registry with available blood samples (180 AGS samples and 104 control samples) as per established methodology [4,42-44]. Preliminary data on this measure demonstrates an improvement in ISG scores in children with AGS before and after treatment with baricitinib (Figure 6).

Measurement of Neurologic Function based on GMFM-88

Individuals affected by AGS can have a range of motoric disability, secondary to direct muscle inflammation (inflammatory myopathy) as well as from injury to the central nervous system. As physical abilities are an essential component of activities of daily living and a major contributor to quality of life, it is important to assess the impact of AGS on motor function. Gross Motor Function Measure (GMFM-88) is a validated outcome measure of motor function in children [45-51]. Depending on the tracts involved and the extent of injury, individuals affected by AGS can have a range of motoric disability from mild lower extremity spasticity to inability to support one's own head. The GMFM-88, administered by trained physiotherapists, covers 5 distinct categories: lying and rolling, sitting, crawling and kneeling, standing, and walking and running. While there are few published studies measuring ambulation and motoric decline in patients with a leukodystrophy, our goal is that these longitudinal motor assessments will aid our understanding of disease progression and facilitate the assessment of drug response. In addition to its initial use in cerebral palsy, GMFM-88 has been utilized across several other disorders, including metachromatic leukodystrophy [52], trisomy 21 [53], and spinal muscular atrophy [54]. Preliminary data demonstrates the feasibility of GMFM-88 in individuals affected by AGS (Figure 7) and responsiveness to therapy. However, during our pilot studies, we determined a significant floor effect in AGS patients using the GMFM-88, with measurable function above 15% of normative values in only a small subset of individuals. Similarly, only a small subset of invididuals had measureable improvement in GMFM-88 during a study period of 6 months or more.

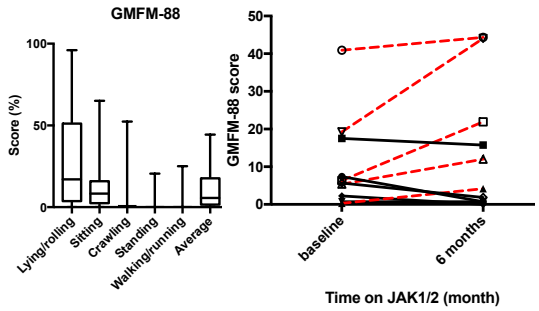


Figure 7: Domain scores for GMFM-88 in 15 children affected by AGS demonstrate the best skills in lying and sitting, and severe deficits in crawling, standing, and walking (left panel). A subset of affected individuals develop improvement after treatment with baricitinib (right panel)

Measurement of AGS Scale

In order to account for these floor effects, in addition to measurement of motor function through the GMFM-88, we will also employ an AGS Scale, which was recently developed by our group.[55,56] Progressive childhood diseases, such as AGS, offer unique complications in that they require the assessment of children with potentially worsening skills superimposed on an evolving panel of predicted developmental

milestones (Figure 8A). This scale allows for assessment of skills (smiling, head control, rolling) as compared to a historical data set of children affected by AGS. Preliminary data using the AGS scale (Appendix 5, Figure 8B), demonstrates responsiveness in our expanded access program in a proportion of individuals. In our compassionate cohort, 11/34 (32%) treated individuals with data available for AGS scale scoring had improvement in the AGS scale after treatment with baricitinib. Response was correlated with AGS scale score at baseline (Table 2) such that in individuals with an AGS scale of 0-3 (Cohort A in proposed study), 6/19 individuals improved (31%), while in those individuals with AGS scale of 4-8 (Cohort B), 5/6 individuals improved by 2 points (83%) and the remaining individual also improved, but only by one point. Notably, none of higher functioning individuals at the upper level of the AGS scale (≥9) (0/9) had improvement on the AGS scale, although this could be attributed to ceiling effect. Notably, some higher functioning individuals (Cohort C) had measurable improvement in GMFM-88, in particular in domain E (walking, running and jumping). This scale is simple enough to be able to be applied retrospectively, based on clinical notes, permitting us to develop a historical control cohort for comparison.

Figure 8A. Developmental milestones are severely delayed in AGS. Individuals affected by AGS are profoundly disabled, with limited functional skills across modalities.

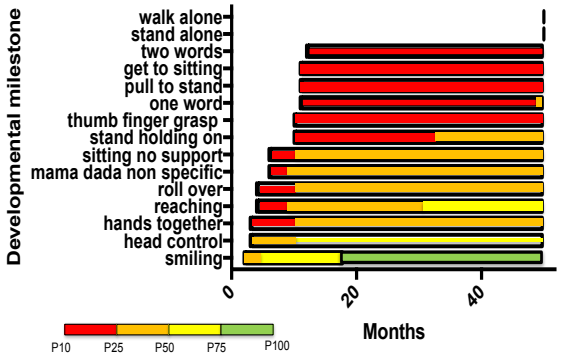
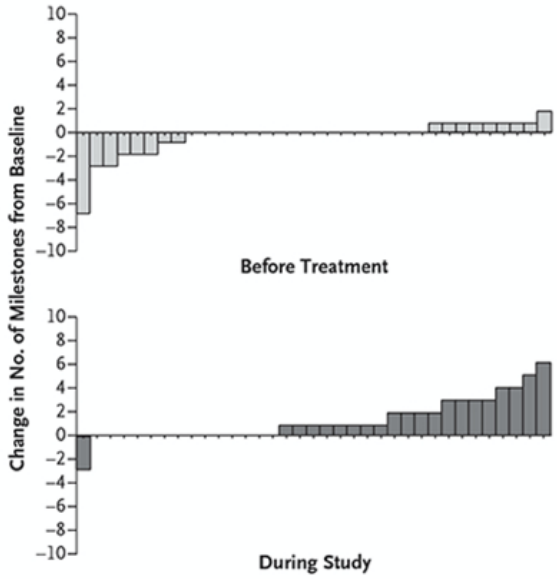


Figure 8B. Pilot data using AGS Scale; AGS scale scores improve following treatement with baricitinib in a majority of individuals.

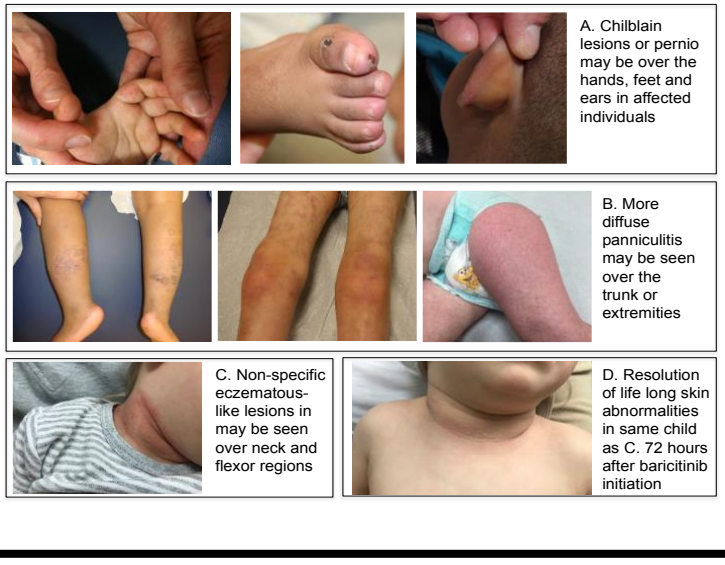


Measurement of Skin involvement using a standardized scale, the CLASI

As one of the most clinically measurable manifestations of AGS is the dermatologic involvement, we have initiated a project to define and quantitate the skin manifestations found in patients with AGS. Aside from neurologic injury, skin manifestations are one of the most common manifestations of AGS, occurring in over 30% of affected individuals [2]. Skin manifestations in AGS are reminiscent of those seen in other rheumatologic disorders, such as systemic lupus erythematosus (SLE). Skin injury can present variably (Figure 9A-C) and appear uniquely responsive to JAK1/2 inhibitors (Figure 9D). The skin ulcerations and chilblains found in individuals affected by AGS are hypothesized to be secondary to an underlying vasculopathy [57-59]. These skin lesions have previously been unresponsive to treatment with steroids or other immune suppressive approaches [2] and anecdotal evidence of their improvement with treatment with JAK1/2 inhibitors are a major argument for clinical benefit using these drugs. In addition, they offer a readily accessible tissue that can be tested for IFN related injury, unlike brain tissue. For this study, investigations will utilize the assessment tool CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index- Appendix 13) before and after treatment with JAK1/2 inhibitor [60].

The connection between skin pathology and IFNs is well established. A single injection of IFN into human skin activates over 700 genes, including multiple chemokines [61]. These IFN-regulated gene products are also up-regulated in chronic inflammatory skin diseases such as atopic dermatitis, psoriasis, and cutaneous lupus. Additionally, treatment of psoriasis with a JAK1/3 inhibitor, tofacitinib, results in the resolution of cutaneous inflammation over a 12-week period [62]. As determined by histology and gene expression measures, this improvement is associated with progressive normalization of IFN-regulated genes, as well as other immune pathways which are indirectly stimulated by IFN activation [62]. Within one month of treatment with tofacitinib, histologic disease features and infiltrating T-cells and DCs are significantly reduced and several IFN-regulated gene products show >10-fold reductions [62]. As hypothesized, in preliminary data, the skin manifestations in AGS have been robustly responsive to baricitinib therapy (Figure 9).

Figure 9. Dermatologic findings in AGS



1.6 Compliance Statement

This study will be conducted in full accordance with all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent, 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

This study is an open-label design using baricitinib in patients with AGS. Subjects will be compared to pretreatment values and historical controls before and after treatment with baricitinib for AGS scale results. Secondary outcomes will also include functional neurologic tests, symptom diary scores, safety parameters and clinical features including skin involvement, and ISG scores. Though the open-label design has potential for the introduction of bias, the study design represents an ethical approach for treatment of AGS given the treatment effect seen in a prior Lilly-sponsored expanded access approach.

2.1 Primary Objective (or Aim)

The primary objective of this clinical study is to determine if the administration of baricitinib to patients with AGS results in improvement or stability of the AGS scale from baseline to 52 weeks after treatment.

2.2 Secondary Objectives (or Aim)

Secondary objectives for this study include:

Determine if the administration of baricitinib to patients with AGS results in an improvement or stability of the AGS scale from baseline through end of study treatment, up to 288 weeks.

Secondary objectives also include assessment of safety parameters including laboratory findings and adverse events.

An additional secondary objective is to determine if the administration of baricitinib to patients with AGS results in improvement of the AGS disease activity scale (daily diary), and of the GMFM-88 post-baseline for up to 288 weeks.

Additional secondary objectives include:

- the stability or improvement of known clinical complications of AGS, including skin manifestations as measured by the CLASI (Cutaneous Lupus Assessment

of Skin Involvement),
- the improvement of a surrogate biomarker, the Interferon Stimulatory Genes (ISG) score, as calculated by Nanostring analysis.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

3.1.1 Transfer of patients from the Compassionate Use Treatment Protocol I4V-MC-JAGA

Subjects enrolled in the Compassionate Use Treatment Protocol I4V-MC-JAGA (JAGA Compassionate Use study, CHOP IRB Study #13205), sponsored by Eli-Lilly, and for whom commercial supply is not available, may be reconsented to the investigator-initiated JAK inhibitor treatment in AGS study. Because the JAGA Compassionate Use study protocol and this protocol are carefully aligned, subjects will continue with the next study visit in their study schedule as planned, as part of their original participation in the JAGA Compassionate Use study. For example, if subjects recently completed visit 212, and are next due for visit 213 three months later, they will complete visit 213 as part of their participation in the investigator-initiated JAK inhibitor treatment in AGS study, without any interruption in the sequence of study visits.

3.1.2 Additional subjects

3.1.2.1 Screening Phase

Participants will be recruited by advertisement via testing laboratories, family advocacy organizations, self-referral, or participation in a clinical leukodystrophy program. Patients' families will be first contacted by non-study personnel to discuss the possibility of participating in a clinical trial. If the patient is also a patient of the investigators, study participation will be discussed with the Medical Monitor. Should the family be interested, patients and families will be invited to contact the investigative team to discuss participation and ICF documents will be shared with the family. Should the family continue to be interested, the family will be invited to visit CHOP.
Potential subjects will be screened using the protocol inclusion and exclusion criteria. Potential subjects can also be pre-screened over the phone. The pre-screening period is described in Section 4.2. As part of the pre-screening period, patients or their guardians will undergo telephone consent, to explain the purpose and procedure of the study. Formal written consent will be obtained at Visit 1. Medical records will be collected for verification of study eligibility, including mutation status, after release of information and after verbal consent for screening. Parental/guardian permission (informed consent) will be obtained prior to any study related procedures being performed. Physical examination, echocardiogram, EKG, CXR, baseline neurologic function testing, and blood samples will be drawn to confirm eligibility based on clinical laboratory parameters. Additional results of blood tests for hematologic, liver, and metabolic parameters will be performed on a research basis for screening purposes. Females after menarche will have a urine pregnancy test.

3.1.2.2 Study Treatment Phase (start of the study intervention)

Eligible patients will be enrolled and initiated on intervention, baricitinib, using open-label treatment, and according to established dosing regimens for weight and eGFR based on age (Appendices 3 and 4). Regular evaluations for safety and efficacy (Appendices 1 and 2) will be performed while on study intervention (see section 4).

3.1.3 Allocation to Treatment Groups and Blinding

This is an unblinded, open-label study. A historical cohort will be used for comparison of the natural history of the AGS Scale.

3.2 Study Duration, Enrollment and Number of Sites

3.2.1 Duration of Study Participation

The study duration per subject will be up to 288 weeks, preceded by a screening period during which baseline testing will be obtained.

Study duration will be extended beyond Week 288 to long term follow up if transition to commercial supply is not possible for the patient.

3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at one investigative site in the United States.
It is expected that up to approximately 55 subjects may be enrolled, including those patients transferred from the JAGA Compassionate Use study (CHOP IRB Study #13205).

3.3 Study Population

Patients who meet all of the inclusion criteria (Section 3.4.1) and do not meet any of the exclusion criteria (Section 3.4.2) may enter the study (that is, sign consent). In addition, patients must meet the enrollment criteria in order to be eligible to receive baricitinib. The enrollment number of up to approximately 55 is an estimate based on the number of subjects required to obtain statistically significant results for efficacy, and accounting for those subjects who are found to be ineligible at screening, subjects withdrawn from participation for various reasons and replaced. The analysis of data obtained from these initially ineligible, but prospectively approved group of subjects entered to the study, will be assessed independently of the main group of subjects who meet all eligibility criteria. The impact of this group of subjects on the statistical analysis of this clinical protocol has been added to Section 6.4, “Sample Size and Power”.

3.3.1 Patients from the Compassionate Use Treatment Protocol 14V-MC-JAGA

Patients previously enrolled in the Compassionate Use Treatment Protocol I4V-MC-JAGA (JAGA Compassionate Use study, CHOP IRB Study #13205) will automatically roll into this study and do not need to meet the eligibility criteria outlined below.

3.3.2 Inclusion Criteria

Identification of individuals appropriate for the study

Eligible patients will meet the following criteria:

- Clinical or molecular identification of Aicardi Goutières Syndrome including the following features
  - CSF or blood markers suggesting elevations of markers of interferon activation including CSF pleocytosis, elevation of interferon, and/or neopterin and tetrahydrobiopterin elevations
  - Evidence of neurologic disease on neuroimaging including intracranial calcifications and or a leukoencephalopathy
  - Clinical features of disease including features such as microcephaly, subacute encephalopathy, myopathy, spastic diplegia, skin involvement, autoimmune hepatitis, hematologic abnormalities
  - OR have documented mutations felt to be pathogenic in an AGS associated gene.
- Are ≥1 month of age.
- Are ≥4.5 kg in body weight.
- Females after menarche must have a negative urine/serum pregnancy test and must use an acceptable method of contraception, including abstinence, a barrier method (diaphragm or condom), Depo-Provera, or an oral contraceptive, for the duration of the study.
- Parental/guardian permission (informed consent).

3.3.2.1 *Inclusion of Minorities and Children*

The disorders to be investigated affect both genders and all different ethnic groups and we therefore expect to have proportional representation among the participants of the trials. These are rare disorders, and we will attempt to recruit all presenting potentially eligible patients. Most persons affected with AGS are children and thus pediatric patients will be included.

3.3.3 Exclusion Criteria

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

- Are pregnant or nursing at the time of entry or unable to use contraception as detailed below
  - Are females of childbearing potential (women >12 or who have had at least one 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 below) or remain abstinent during the study and for at least 28 days following the last dose of investigational product
  - Are sexually active males who do not agree to use 2 forms of highly effective birth control (see below) 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.
  - 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)

- Overall health status that in the opinion of the investigator limits the safety of the use of baricitinib.
- 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, with the exception of oral rotavirus vaccinations for which the time period is 2 weeks. 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 a documented conversation by a physician not affiliated with the study or the Medical Monitor with the parents to ensure parental consent and understanding of the risk/benefit ratio of not receiving scheduled vaccinations. These subjects will only be included in the study after a physician obtaining consent also describes the risk/benefit ratio of not receiving scheduled vaccinations.
- Have the following evidence of renal insufficiency:
    - An estimated glomerular filtration rate (eGFR) based on the most recent available serum creatinine of <40 mL/min/1.73 m^2 if greater than 2 year of age. eGFR will be calculated using the *Bedside Schwartz Equation:* eGFR (mL/min/1.73 m^2) = (0.413 x height) / $S_{Cr,}$ with height measured in cm, and serum creatinine (S_{Cr}) in units of mg/dL.
    - Children with an eGFR of <40 mL/min/1.73 m^2 will not be enrolled, unless <24 months of age in which case a cut off of <30 ml/min/1.73 m2 will be used due to age-based differences in normal eGFR. Normal eGFR of <60 ml/min/1.73 m^2 is common in children <12 months, and a normal eFGR <40 ml/min/1.73 m^2 is common in infants <3-6 months.
    - The creatinine should be measured using the IDMS (Isotopic Dilution Mass Spectrometry) technique to monitor the eGFR if available. Other methods are allowed but are not preferred. Laboratory testing using other methods will not be used to monitor the eGFR.
- Have any of the following specific Hematologic abnormalities on screening laboratory tests (Appendices 10, 11, 12):
    - Hemoglobin <7 mg/dL (70 g/L). In infants <2 mo of age, 8 mg/dL will be used as a threshold
    - Neutropenia (absolute neutrophil count [ANC] <500 cells/µL)
    - CD4 <250 cell/µl on lymphocyte subset testing (where Absolute CD4 count=Absolute CD3/CD4 count=CD3/CD4 count=CD4 count=Absolute CD3+CD4+ cells)
    - Thrombocytopenia (platelets <30,000/µL). Patients who are on

anticoagulation or having a history of life-threatening bleeding should be excluded if platelet count is <50,000/μL

- Have any of the following infectious risks:
    - 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
    - Ongoing or incompletely treated severe or systemic infection, excluding cellulitis/osteomyelitis that is felt to be attributable to AGS
    - Have had symptomatic herpes zoster infection within 12 weeks prior to entry or during the screening period
    - Have a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, central nervous system involvement or systemic involvement including hepatitis or pneumonitis)
    - Have a history of active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
    - Have had household contact with a person with active tuberculosis (TB) and did not receive appropriate and documented prophylaxis for TB
- 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.
- Have liver abnormalities consistent with severe, chronic liver disease (Appendix 9).
- Have ECG or echocardiogram results that include an arrhythmia unamenable to standard treatment, severe pulmonary hypertension, severe heart valvular (greater than mild insufficiency or stenosis), or significant left heart failure (per AHA guidelines, an LVEF <50% is considered impaired) or right heart failure (RV function described as qualitatively more than mildly diminished systolic function), that in the consideration of the investigator places them at greater risk for participation in the study; 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); have echocardiogram results that, in the opinion of the investigator, places them at greater risk if included in the study.
- Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures.
- 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 is not indicated in subjects receiving Natalizumab, Nivolumab, Trastuzumab, Denosumab, and Belimumab. Use of IVIg is permitted.
- Have received or be currently treated with BCG (Intravesical), Cladribine, Dipyrone, Pimecrolimus, and Tacrolimus (Topical).

- 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.
- 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 and are not attributable to AGS.
- 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.
- 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. The patient may also have a QuantiFERON®-TB Gold test. If the test is positive or indeterminate, the patient may undergo evaluation including a CXR and PPD and assessed for likely risk of active tuberculosis infection. In infants < 12 months of age, maternal and paternal testing can be used instead of testing the patient. Risk for TB will also be assessed using validated questions from The Red Book: Report of the Committee on Infectious Diseases (see below).

  Validated Questions for Determining Risk of LTBI in Children in the United States

  - Has a family member or contact had tuberculosis disease?
  - Has a family member had a positive tuberculin skin test result?
  - Was your child born in a high-risk country (countries other than the United States, Canada, Australia, New Zealand, or Western and North European countries)?
  - Has your child traveled to a high-risk country? How much contact did your child have with the resident population?

- 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. In infants < 3 months of age, maternal testing can be used instead of testing the patient.

- 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. In infants < 12 months of age, maternal testing can be used instead of testing the patient.
- Have HIV virus. In infants <12 months of age, maternal testing can be used instead of testing the patient.
- Taking a concomitant medication on the list of exclusion criteria (Appendix 16).

4 STUDY PROCEDURES

4.1 Unforeseeable emergency events

In some circumstances, unforeseeable events, such as public health emergencies, states of emergency related to civil unrest, or weather emergencies, or individual health emergencies (affecting the patient or a caregiver), may create situations where it is unsafe for patients and their families to travel to the study site for in-person assessments. In that case, the visit will be conducted using video operations. The changes from an in-person evaluation, including differences to the study outcome collection, will be reported as a minor protocol deviation to the IRB at the time of continuing review.

4.2 Pre-screening period

The pre-screening period is applicable only to subjects not transferred from the JAGA Compassionate Use study (CHOP IRB Study #13205). The pre-screening period is a period from 2 weeks to 6 months during which the study will be discussed with the patient and caregivers. During this time, the study team may discuss the study with patients and families, and records of clinically indicated studies will be collected to help determine potential eligibility during the screening process. Individuals will undergo this pre-screening period if insufficient information about prior clinical care is available to the study team, for example, if their clinical care is received outside of the regional area. As part of the pre-screening period, patients or their guardians will undergo telephone consent, to explain the purpose and procedure of the study. Formal written consent will be obtained at Visit 1. During this period, blood and urine will be collected and daily diaries completed.

4.3 Screening Visit

Screening (Visit 1) is applicable only to subjects not transferred from the JAGA Compassionate Use study (CHOP IRB Study #13205). The screening visit is a 2- to 28-day period beginning at Visit 1. After receiving written informed consent from the patient's parent or a legal guardian (hereafter, "parent" refers to "parent or legal guardian"), 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 (Appendices 1 and 2). 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 and Appendices 5 and 6). Current use of concomitant medications and reasons for use will also be collected on the eCRF, as well as start and stop dates. Particular note will be made of medications that are contraindicated (see Section 3.4.2) and which require dose adjustment (see Section 4.4).

4.4 Study Treatment Phase

4.4.1 Enrollment

Consent

Written informed consent from the patient/patient's parent or a legal guardian will be obtained in person by the study investigators prior to any study procedure, with the exception of blood and urine tests, and daily diaries, which may be completed from the pre-screening period, after verbal consent.
For the patients transferred from the JAGA Compassionate Use study (CHOP IRB Study #13205), written informed consent from the patient/patient's parent or a legal guardian will be obtained by the study investigators prior to any study procedure completed as part of this investigator-initiated study.
Additionally, all the JAGA subjects (including the patients who do not consent and transition to the investigator-initiated JAK inhibitor treatment in AGS study will be asked to sign a consent form to allow for their data collected as part of the compassionate use program to be used for data analysis as part of the investigator-initiated study. The JAGA subjects who do not transition to the investigator-initated study will sign a separate consent form while the subjects who transition will be re-consented with a revised informed consent form including mention of this data transfer. Statistical considerations of this data transfer are detailed in Section 6.

Inclusion criteria

Entered patients are eligible for enrollment into the study (that is, eligible to receive baricitinib) only if they meet inclusion criteria (Section 3.4.1) at the time of Visit 2 and don't meet the exclusion criteria listed in Section 3.4.2.

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 exclusion criteria listed in Section 3.4.2.

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. Patients will receive treatment as clinically indicated for infections regardless of treatment decisions for baricitinib.

Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion excludes individuals with concomitant medical conditions that increase the risk for their participation in the study, who may not be compliant with study-related procedures or whose participation in the study may introduce bias.

Discontinuation of patients after enrollment if criteria are not met

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.

4.4.2 Initial Treatment and Dose Escalation

Baricitinib will be dosed by patient age, weight range and eGFR. See Appendix 3 for the dosing schedule for patients with eGFR ≥60 mL/min/1.73 m^2 or normal eGFR for patients age <24 months (eGFR ≥60 mL/min/1.73 m^2). eGFR will be calculated using the *Bedside Schwartz Equation:* eGFR (mL/min/1.73 m^2) = (0.413 x height) / $S_{Cr,}$ with height measured in cm, and serum creatinine (S_{Cr}) in units of mg/dL. The creatinine should be measured using the IDMS (Isotopic Dilution Mass Spectrometry) technique to monitor the eGFR if available. Other methods are allowed but are not preferred. Laboratory testing using other methods will not be used to monitor the eGFR. Tolerance will be judged by stability or improvement in hematology and chemistry laboratory test results collected as specified in Study Schedule (Appendices 1 and 2). See Appendix 4 for the dosing schedule for patients with eGFR 30 - <60 mL/min/1.73 m^2 or patients <24 months with abnormal eGFR (eGFR 30 - <60 mL/min/1.73 m^2).

Patients must receive a dose for at least 72 hours before a dose escalation can occur. Safety laboratory data will be assessed according to the Study Schedule (Appendices 1 and 2).
Every effort should be made to follow the dose escalation schedule shown in Appendices 3 and 4. However, if a patient's condition warrants an accelerated dose escalation schedule, dose reduction, interruption, or discontinuation, this may be allowed after review of the patient's clinical data and consultation with the sub-investigators. Additionally, in the event of AEs possibly attributable to the study drug, the dose may need to be reduced. These decisions should be taken following documented consultation, and agreement between the investigator and sub-investigators, and approval from the IRB prior to initiating the dose modification. Only in emergency situations will the investigator take subsequent dose restarts or increments after review of clinical data, documented agreement between the investigator and sub-investigators, and notification of the IRB.

Attention will be given to concomitant medications, in particular those that are exclusion criteria (Appendix 16).
Where needed, clinical pharmacists will be contacted about the need for dose adjustment and for guidance related to concomitant therapies that must be used with caution.

In the event that it is necessary to contact a clinical pharmacist, the study team can page the 24/7 on-call clinical pharmacist.

Pharmacokinetic Sampling: Blood samples will be collected to determine baricitinib concentrations. Samples will be collected after beginning baricitinib therapy and at each dose increase at the time points shown in the Study timeline and may be collected at each study visit for safety monitoring. In these cases, PK sampling will occur at least 72 hours after dosing changes or at the next visit. PK testing may include a single measurement at 1.5 hours, or a full PK series at baseline, 1.5 hours and 4 hours post dose, and may include several doses during the day (eg morning and afternoon dose). For PK series, an IV will be placed. For single PKs, these will be drawn with the safety laboratory monitoring. PK samples may be banked for later analysis.
As PK data become available, dosing adjustments may be required.
Finally, changes in a subject's weight or renal function may require dose changes as the individual falls within different categories in the tables in Appendices 3 and 4. For example, this may occur in a child under 1 year of age with rapid weight gain.

4.5 Continuing treatment

4.5.1 Continuing treatment for patients transferred from the JAGA Compassionate Use study

After consent to the investigator-initiated JAK inhibitor treatment in AGS study, transferred patients will undergo review of the patient's clinical condition, AEs, and blood tests for safety by the Principal Investigator. Safety laboratory assessments will be reviewed by the investigator along with a copy of the patient's diary, AEs and concomitant medications. If the patient is responding adequately to treatment (average diary score <0.5) or reduction in average diary score, the patient will continue receiving baricitinib therapy with follow-up appointments according to the Study Schedule (Appendices 1 and 2), based on the timelines of the most recent study visit on the JAGA Compassionate Use study (CHOP IRB Study #13205). If the patient is responding to treatment, but has not yet reached symptom control, dose escalation may be performed as discussed above and in Appendices 3 and 4. 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]).

4.5.2 Continuing treatment for patients originally consented to this study

After the patient has received baricitinib at the target dose level, 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 (Appendices 1 and 2). 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. If the patient is responding adequately to treatment (average diary score <0.5) or reduction in average diary score, the patient will continue receiving baricitinib therapy with follow-up appointments according to the Study Schedule (Appendices 1 and 2). If the patient is responding to treatment, but has not yet reached symptom control, dose escalation may be performed as discussed

above and in Appendices 3 and 4. 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]).

This section also applies to patients who continue treatment beyond Week 288.

4.6 Immunosuppression monitoring during continuing treatment

Recent data has clarified that subjects with AGS are at risk of hematologic disturbances, including neutropenia[63]. In addition, baricitinib is associated with neutropenia and leukopenia. However, AGS subjects treated with baricitinib typically have transient neutropenia and leukopenia that is not clinically significant[63]. As part of ongoing safety monitoring, we will continue to assess every 3 months the following laboratory studies: T cell subsets, immunoglobulins and CBC with differential. If these tests are all normal (CD4 >250 cell/μl, ALC (Absolute lymphocyte count)>500/mm^3, IgG >400mg/dL, ANC (Absolute Neutrophil Count) >1000/mm^3), we will continue to follow immune function every 3 months.
If individuals have abnormalities on ANY of the proposed testing (CD4 <250 cell/μl, ALC <500/mm^3, IgG <400mg/dL, OR ANC <1000/mm^3), following management plans will be put in place and prophylaxis initiated (Appendix 10).

a. Patients will be followed as per Appendix 10 with repeat CBC and immune phenotyping and drug tapering or discontinuation considered as per Appendix 14.
b. For persistent abnormalities, patients will be clinically referred to an immunologist for clinical care with their local care team and will be asked to continue to clinically follow with this expert for immunosuppression as defined by CD4 <250 cell/μl, ALC <500/mm^3, IgG <400mg/dL, OR ANC <1000/mm^3.
c. Prophylactic approaches will also be put in place if patients on baricitinib have persistent abnormalities meeting specific criteria (Appendix 10).

4.7 Concomitant Medication

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

After starting baricitinib, if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, tapering from protocol therapy occurs at start of or before the new agent is started. This is considered an event in the statistical analysis. Exceptions to this rule:
1. Topical and inhaled corticosteroids are allowed.
2. Pulses of corticosteroids (prednisone, hydrocortisone, dexamethasone, or methylprednisolone) at any dose for less than 7 days (consecutive or cumulative) in a 28-day window are allowed.
3. Daily hydrocortisone for adrenal insufficiency is allowed.
4. Treatment for immune mediated hemolytic anemia or Immune mediated thrombocytopenia is allowed.
5. If a patient is enrolled and is taking immune suppression at the time of initiation of baricitinib and stops this other immune suppressant for any reason, that immune suppressant can be restarted.

Use of other concomitant medications will follow the parameters outlined in Appendix 16.

4.8 Dosing changes

On occasion, if drug related adverse events are seen, changes or discontinuation of study medication will be considered. Because abrupt drug discontinuation may result in rebound inflammation, tapering of dosing to the next dosing increment (e.g. 2 mg three times a day to 2 mg twice a day – Appendix 14) may be considered in response to suspected drug related adverse events. Repeat laboratory testing will be performed after drug tapering and results will be discussed with the study team to assess that drug continuation at a lowered dose is in the best interest of the patient.

4.9 Subject Completion/Withdrawal

On occasion, the investigator may find it necessary to decrease (Appendix 14), temporarily interrupt or prematurely permanently discontinue investigational product administration following the occurrence of an AE or an abnormal laboratory finding. The investigator must notify the DSMB within 48 hours when decreasing, temporarily interrupting or prematurely permanently discontinuing therapy for an individual. If infection is the cause of the interruption, patients will receive treatment as clinically indicated for infections regardless of treatment decisions for baricitinib.
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.
- 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.
- The investigator decides that the patient should be withdrawn from the study.
- The parents, legal guardian, or patient requests to be withdrawn from the study.
- Investigational product is no longer supplied.

4.9.1 Early Termination Study Visit

Subjects who withdraw from the study will have all procedures enumerated for the early termination visit as per the study schedule and timeline (Appendices 1 and 2) either in person or by telephone visit.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations: Performed as Part of Clinical Care

5.1.1 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 (Study Schedule in Appendices 1 and 2). Fundoscopy may be completed as part of the physical exam if complaints of headache are present or irritability worsens on medication, and ophthalmology may be consulted as clinically indicated.

5.1.2 Vital Signs

Vital signs (blood pressure and pulse) will be measured at times indicated in the Study Schedule (Appendices 1 and 2). Any clinically significant findings that result in a diagnosis should be captured on the eCRF and reported as an AE. Additional measurements of vital signs may be performed at the discretion of the investigator.

5.1.3 Cardiac monitoring

Pulmonary hypertension (PH) is a rare but potentially fatal disorder characterized by severe vasculopathy and elevated pulmonary artery pressures leading to right-sided heart failure. Progressive PH has both genetic and inflammatory influences [28-34]. In particular, type I interferons, as are overexpressed in AGS, have been established as risk factors for the development of PH [29,35-38]. We have identified several individuals within our cohort with PH, as related to systemic interferon overexpression (paper submitted). Cardiac involvement will be quantified using clinical assessment and echocardiogram. As per World Health Organization (WHO) guidelines, PH will be defined as persistently elevated mean pulmonary arterial pressure of ≥25 mmHg and a pulmonary capillary wedge pressure of ≤15 mmHg for precapillary PH [64]. In setting of contraindication to cardiac catheterization (e.g. critical illness), combined echocardiographic and clinical evidence of PH will be utilized [65]. Individuals affected by AGS will have screening cardiac evaluations every other year, unless abnormalities are noted, on a clinical basis, with additional management as clinically indicated. If not previously performed on a clinical basis, this may be performed on a research basis. In the patients identified as being affected by PH, we will follow the relationship between PH, and the response to baricitinib.

5.1.4 Electrocardiograms

Twelve-lead ECGs will be obtained clinically during the screening process. A single 12-lead ECG measurement will be performed at screening. Subsequently, ECGs will be obtained every other year as a part of clinical care to screen for pulmonary hypertension, in addition to echocardiograms every other year as discussed above. If not previously performed on a clinical basis, this may be performed on a research basis.

5.1.5 Chest X-ray and tuberculosis screening

During the screening process, we will review clinically obtained posterior-anterior view chest x-ray obtained within 6 months prior to the study. 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 as described above.

5.1.6 Laboratory Evaluations

Appendix 2 lists the schedule for sample collections in this study. Appendix 8 lists the specific tests that will be performed for this study. Some testing may occur outside of inperson study visits at CHOP and these will be considered as being performed as part of clinical care.
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, as well as limited PK studies. These will be considered as being performed as part of clinical care.

5.1.7 Medical Record Review

Include a listing of the variables that will be abstracted from the medical chart (paper or electronic).
Date of birth
Date of symptom onset
Symptom complex at symptom onset
Date of diagnosis
Genotype
MRI and CT findings
Weight
Height
Head circumference
Prior health events
Prior and concomitant medications
Level of baseline neurologic function (rolling, sitting, ambulation, speech etc).

5.1.8 Pregnancy Testing

A pregnancy test will be performed (if applicable).

5.2 Screening and Monitoring Evaluations: Performed as a Part of Research

5.2.1 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 (Study Schedule in Appendices 1 and 2). Fundoscopy may be completed as part of the physical exam if complaints of headache are present or irritability worsens on medication, and ophthalmology may be consulted as clinically indicated.

5.2.2 Vital Signs

Vital signs (blood pressure and pulse) will be measured at times indicated in the Study Schedule (Appendices 1 and 2). Any clinically significant findings that result in a diagnosis should be captured on the eCRF and reported as an AE. Additional measurements of vital signs may be performed at the discretion of the investigator.

5.2.3 Symptom Diaries

Symptom diaries are to be completed for at least two years from treatment initiation. Refer to Appendices 6 and 7 for symptom diaries.

5.2.4 AGS Scale

Refer to Appendix 5 for AGS Scale, which will be applied at baseline, 3 months, 6 months, 9 months,12 months and every subsequent study visit through neurologic exam and conversation with parents.

5.2.5 GMFM-88

Individuals affected by AGS can have a range of motoric disability, secondary to direct muscle inflammation (myositis) as well as from injury to the central nervous system. The GMFM-88, administered by trained physiotherapists, covers 5 distinct categories: lying and rolling, sitting, crawling and kneeling, standing, and walking and running. Preliminary data demonstrates the feasibility of GMFM-88 in individuals affected by AGS (Figure 7). We will continue these serial assessments and compare the GMFM-88 scores to the clinical diaries, skin manifestations, and IFN signature scores, as described elsewhere.
Composite scores for the GMFM-88 will be calculated [25,46,66] and compared to normative data. Additionally, domain and subdomain scores will be recorded as raw and standardized scores. Functional measures developed for typically developing or mildly affected children (cerebral palsy) have not been validated in severe disorders such as AGS. However, our preliminary data suggests that these measures are reliable measures in AGS subjects.

The GMFM-88 may be performed remotely, via video assessment. The remote assessments will be performed by trained therapists that will administer the assessment and score the performance live, having the patients' parents assisting their children if needed according to a published, validated approach[67].
The families will be provided with information prior to the research encounter regarding the necessary environment and technology needed for home evaluations, as included in the following table:

Small bench smaller than 3’ (feet touch floor when sitting)
Large bench to stand and cruise
12”-24” stick
Large object to carry with two hands (soccer ball or similar)
5 steps/rail
2 straight parallel lines 20’ x ¾’ and 20’ x 8”
24” circle

Sessions will be conducted over a secure video conferencing platform (e.g.: Cisco WebEx/BlueJeans/myCHOP). Existing home equipment, including typical home furniture, will be selected to be as close as possible to the standard equipment and for subsequent evaluations and logged for consistency, in accordance with the GMFM-88 manual. All 88 items will be administered during the virtual encounter. Session will be recorded with a fixed camera angle.

5.2.6 AGS Development

In addition to formal measurement of motor function through the AGS scale and the GMFM-88, we will also employ descriptive approaches to assess typical developmental milestones. Progressive childhood diseases, such as AGS, offer unique complications in that they require the assessment of children with potentially worsening skills superimposed on an evolving panel of predicted developmental milestones. This scale allows for assessment of skills (smiling, head control, rolling) as compared to the average (P50) child affected by AGS, as opposed to age-matched controls (Figure 2). We will assess the longitudinal benefit of baricitinib on the rate of acquisition of skills in the domains of motor, speech and manual abilities. These scales can be applied using historical data acquired during clinical encounters with validated functional tools including the gross motor function classification system (GMFCS), manual ability classification system (MACS), communication function classification system (CFCS), and the Eating and Drinking Ability Classification system (EDACS) [68].

5.2.7 Skin Inflammation

As one of the most clinically measurable manifestations of AGS is the dermatologic involvement, we have initiated a project to define and quantitate the skin manifestations found in patients with AGS. Aside from neurologic injury, skin manifestations are one of the most common manifestations of AGS, occurring in over 30% of affected individuals[2]. As hypothesized, in our preliminarily results, the skin manifestations in AGS have been robustly responsive to baricitinib therapy (Figure 3).
Additional investigations will utilize the assessment tool CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) before and after treatment with JAK1/2 inhibitor. The dermatologic findings will be correlated with measures of neurologic function and the clinical diary as described above. The skin ulcerations and chilblains found in individuals affected by AGS are hypothesized to be secondary to an underlying vasculopathy [57-59]. All AGS subjects will undergo a standardized dermatologic evaluation as well as the CLASI, a validated measurement instrument for skin disease (Cutaneous Lupus Erythematosus Disease Area and Severity Index)[60].

This scale has established content validity and reliability [60,69] and was developed in collaboration with our collaborator Dr. Treat who is experienced in its application and analysis. It has since been used extensively in clinical trials in SLE [39,40,70-73], and appears responsive to treatment. These evaluations will be performed by 2 independent clinicians for each assessment. Any patient identified as having skin abnormalities (expected approximately 30% [3]) will be referred for a full dermatologic evaluation.

5.2.8 Cardiac monitoring

Pulmonary hypertension (PH) is a rare but potentially fatal disorder characterized by severe vasculopathy and elevated pulmonary artery pressures leading to right-sided heart failure. Progressive PH has both genetic and inflammatory influences [28-34]. In particular, type I interferons, as are overexpressed in AGS, have been established as risk factors for the development of PH [29,35-38]. We have identified several individuals within our cohort with PH, as related to systemic interferon overexpression (paper submitted). Cardiac involvement will be quantified using clinical assessment and echocardiogram. As per World Health Organization (WHO) guidelines, PH will be defined as persistently elevated mean pulmonary arterial pressure of ≥25 mmHg and a pulmonary capillary wedge pressure of ≤15 mmHg for precapillary PH [64]. In setting of contraindication to cardiac catheterization (e.g. critical illness), combined echocardiographic and clinical evidence of PH will be utilized [65]. Individuals affected by AGS will have screening cardiac evaluations every other year. If not previously performed on a clinical basis, this may be performed on a research basis. In the patients identified as being affected by PH, we will follow the relationship between PH, and the response to baricitinib.

5.2.9 Electrocardiograms

Twelve-lead ECGs will be obtained clinically during the screening process. A single 12-lead ECG measurement will be performed at screening. Subsequently, ECGs will be obtained every other year as a part of clinical care to screen for pulmonary hypertension, in addition to echocardiograms every other year as discussed above. If not previously performed on a clinical basis, this may be performed on a research basis.

5.2.10 Chest X-ray and tuberculosis screening

During the screening process, if no chest x-ray was done clinically within 6 months prior to the study, chest x-ray will be done as part of the research study. 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 as described above. If this has not been done clinically, in the context of standard of care, this will be done on a research basis.

5.2.11 Bone growth monitoring

Animal studies have elicited concerns about bone growth in juvenile animals. Height and weight will be monitored every 6 months. If patients are <1%, they will be referred to their local pediatric team for clinical management. Bone growth monitoring will be performed to include hand/wrist/fingers X-rays at baseline, 6 months, 12 months and

then every 12 months as long as there are no radiographic concerns. The hand is placed on or up against a hard plate while a camera-like machine is placed opposite of the plate. This machine sends a very small burst of radiation which passes through the hand and creates images on the recording plate. IGF-1 will be completed yearly with safety labs. This will be completed on a research basis. With IGF-1 abnormalities, or radiographic concerns for accelerated bone growth, we will refer to bone health team for clinical monitoring.
Hand/wrist/fingers X-rays and IGF-1 testing will not be completed after a bone age demonstrating complete growth.

5.2.12 Laboratory Evaluations

Appendix 2 lists the schedule for sample collections in this study. Appendix 8 lists the specific tests that will be performed for this study. The blood volume frequencies will not exceed the volumes permitted by the NIH (no more than 5 mL/kg may be drawn for research purposes in a single day and no more than 9.5 mL/kg may be drawn over any eight-week period for children, and no more than the lesser of 10.5 mL/kg or 550 mL may be drawn for research purposes over an 8-week period for adults).
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, as well as limited PK studies. If not previously performed on a clinical basis, this may be performed on a research basis.

5.2.12.1 Samples for Standard Laboratory Testing

Blood and urine samples will be collected at the times specified in the Study Schedule (Appendices 1 and 2). Standard laboratory tests, including chemistry, hematology, and urinalysis panels, will be performed. Every effort should be made to obtain all laboratory tests listed in Appendix 8. Missing laboratory testing will be reported in aggregate to the IRB during continuing reviews. The blood volume frequencies will not exceed the volumes permitted by the NIH.
Standard age based pediatric norms will be used to assess out of range values for laboratory testing.
Additional blood samples may be drawn if needed for safety purposes and/or if warranted. Investigators must document their review of each laboratory safety report.

Liver-Function Monitoring
Liver-function monitoring will occur frequently throughout the study. It should be noted that approximately one-third of individuals with AGS have elevations of AST and ALT that are consistent with hepatitis at baseline (AST and ALT fold increase of 3 times and GGT fold increase of 2.5 times from upper limit of normal). Thus, use of standard metrics such as the Recommended Hepatic Evaluation Guidance Document are difficult to apply in this population. If elevations in ALT/AST or total bilirubin occur from the patient's baseline, the patient should be closely observed in consultation with study staff with expertise in hepatology and the Management of Liver Enzyme Laboratory Values (Appendix 9).

Other safety monitoring
Other clinical safety testing, including CBC, renal function and infectious testing will be discussed with study team and the clinical care providers.

5.2.13 Safety Evaluation

Subject safety will be monitored by adverse events, vital signs, physical examinations, and laboratory data (Appendices 2 and 8). Interruption of intervention will be considered in consultation with the study team and the clinical care providers (Appendices 9, 10, 11, 12).

5.2.14 Administration of Study Drug

Study drug will be administered as described in Section 4, and in Appendices 3 and 4, of the protocol.

5.2.15 Medical Record Review

Include a listing of the variables that will be abstracted from the medical chart (paper or electronic).
Date of birth
Date of symptom onset
Symptom complex at symptom onset
Date of diagnosis
Genotype
MRI and CT findings
Weight
Height
Head circumference
Prior health events
Prior and concomitant medications
Level of baseline neurologic function (rolling, sitting, ambulation, speech etc).

5.2.16 Pregnancy Testing

A pregnancy test will be performed (if applicable).

5.2.17 Pharmacokinetic Evaluation

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 the Study timeline and may be collected at each study visit with blood sampling for safety monitoring. In these cases, PK sampling will occur at least 72 hours after dosing changes or at the next visit.
PK testing may include a single measurement at 1.5 hours, or a full PK series at baseline, 1.0 hours, 1.5 hours and 4 hours post dose, and may include several doses during the day (eg morning and afternoon dose). For PK series, an IV will be placed.

For single PKs, these will be drawn with the safety laboratory monitoring. PK samples may be banked for later analysis.
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 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. The assay may be performed at a later time. Samples will be kept in storage at a laboratory facility designated by the Sponsor. If the blood volumes required for PK sampling exceed established local guidelines for phlebotomy, then the PK sample collection may be modified.

5.2.18 IFN Signaling Gene Score

IFN scores are based on mRNA expression of IFN signaling genes (ISG) and represent a surrogate marker for autoinflammation in a variety of disorders [39-41]. IFN scores based on mRNA expression of ISGs have been used to assign a severity score of autoinflammation in a variety of disorders, including AGS [4] and systemic lupus erythematous [39,40]. We will measure ISG in individuals affected by AGS as per established protocol [4,42,43]. ISG scores will be calculated for all AGS affected individuals in the MDBP registry with available blood samples (180 AGS samples and 104 control samples) as per established methodology [4,42-44]. In brief, copy number of mRNA transcripts of the six type I IFN-inducible genes (*IFI27*, *IFI44L*, *IFIT1*, *ISG15*, *RSAD2*, and *SIGLEC1*) [4] and four housekeeping genes (*ALAS1*, *HPRT1*, *TBP*, and *TUBB*) are quantified using Nanostring nCounter™ Digital Analyzer. The raw copy number of mRNA transcripts of each type I IFN-inducible gene is standardized (stdGene) using the geometric mean of the four housekeeping genes for each individual. The six-gene IFN signature in each individual is calculated using the median of the Z scores. The IFN signature is considered positive (IFN high) if the value is ≥1.96 (>98centile) (one tail analysis). This test is a research test performed in a non CLIA approved laboratory, and will not be used to make clinical decisions around enrollment or patient management.

5.2.19 Leftover Samples for Future Research

Samples obtained during the course of this research project that represent leftover biological samples, will be stored by the sponsor and analyzed in the future, based on scientific questions that may arise during the course of the project.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint will be the change in the AGS scale from baseline to 52 weeks.

6.2 Secondary Endpoints

Secondary endpoints will include the following:

- Improvement of the AGS scale from Screening to Treatment over time.
- Improvement of the GMFM-88 between Screening and Treatment over time.
- The change in Interferon Signaling gene score between Screening and Treatment over time.
- The change in skin symptoms between Screening and Treatment over time using the CLASI.
- Safety and tolerability of DRUG based on Adverse Events (including laboratory abnormalities).
- Change in AGS disease severity score (daily diary) between Screening and two years of treatment.

6.3 Statistical Methods

6.3.1 Baseline Data and Descriptive Analysis

Baseline and demographic characteristics will be summarized overall by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).
In addition, demographic characteristics and clinical variables that are evaluated at the first encounter will be compared between subjects who are never treated, versus those who are eventually treated. Patients are not randomized to receive treatment (or not), so it is important to identify variables that are associated with an increased (or decreased) likelihood of receiving treatment. Chi-square tests will be used to compare categorical variables between groups. T-tests or tests of medians (for skewed variables) will be used to compare continuous variables between groups. Overlaid histograms will also be used to evaluate the distribution of continuous baseline variables between patients who were never treated, versus those who were eventually treated.
In addition, Kaplan-Meier analysis with the log rank test will be used to compare the distribution of time to treatment between levels of categorical variables (e.g. group genotype) measured at baseline. In our preliminary analysis, we did not identify meaningful differences between patients who were never treated, versus those who were eventually treated.
We will conduct descriptive statistical analysis using inferential and graphical secondary data analytic techniques. The primary and secondary assessments will first be summarized by time of measurement. In addition, individual “spaghetti” plots will be generated for each assessment. Changes in primary and secondary outcomes from baseline (with 95% confidence intervals [CI]) will be calculated at specified time points, e.g. between baseline and 52 weeks. In addition, overall changes (final minus baseline) (with 95% CI) will be computed for primary and secondary outcomes. In addition to means (with 95% CI) we will also calculate median changes (with 25^{th} to 75^{th}

percentiles). Analyses will be conducted in Stata 18.0, with a p-value < 0.05 as the criterion for statistical significance.

6.3.2 Primary Outcome Analysis

As is often the case in a study of a rare disease, we face a number of challenges in our analysis. The number of available patients with AGS is limited, so that our sample size is small. This protocol grew out of a compassionate use trial, so that randomization could not be employed to assign patients to receive treatment (or not). The temporal spacing of measurements differs between treated patients versus historical controls. As a result of these features, there are limitations to many of the standard statistical approaches. Our approach will therefore be to apply a recommended approach for efficacy, but to also apply several sensitivity analyses. Our goal will be to demonstrate efficacy for several statistical approaches, as we achieved in our analysis of preliminary data.

Our efficacy analysis for our primary outcome will apply the method described in Section 15.4 of Fitzmaurice, Laird, & Ware[74] that decomposes longitudinal effects of treatment versus cross-sectional effects due to participants starting treatment at different ages. We will first create a time for each patient that is negative prior to treatment and is positive after treatment. We will then fit a GEE model that includes time within patients, an indicator variable for treatment and a time by treatment interaction term. If the interaction term is significant, this will indicate that the change over time in AGS score (slope) is different after treatment, versus before. If the interaction term is not significant, it will be removed and the model will be fitted with time and the indicator variable for (post) treatment. If the indicator variable differs significantly from zero, this will indicate that the AGS score is higher on average, post-treatment. To compare values at baseline and 52 weeks post baseline, different parameterizations of time (continuous versus indicator variables at different visits) will be considered and analyses will also be performed on data restricted to values measured at baseline and 52 weeks post baseline. This approach will first be applied to patients who are eventually treated, to compare their AGS scores pre versus post-treatment.

6.3.3 Secondary Outcome Analysis

6.3.3.1 Longitudinal analysis of the AGS scale

In secondary analysis, we will include historical controls in the GEE models described in section 6.3.2; the “age at treatment” (time zero) for controls will be their age at their final encounter. The GEE models will also adjust for confounders (e.g. age of the subject, length of disease, and genotype[75]) especially variables that were identified as being related to receiving treatment (see Section 6.3.1). We will fit several working correlation structures to model the association between the repeated measurements on each patient, and will use goodness of fit criteria for GEE to choose between the structures. Goodness of fit criteria will also be used to compare fit of models (e.g. for models that include time as a continuous variable versus a series of indicator variables for visit).

In addition to GEE, we will fit quasi-least squares (QLS) regression models.[76] QLS is a computational approach for estimation of the correlation parameters in the framework of GEE that can be applied should GEE fail to converge, or to fit correlation structures that are not available in the framework of GEE. For example, the Markov correlation structure that is plausible for unequally spaced data is not available in the **xtgee** command for implemention of GEE in Stata.

In addition to the GEE analysis that includes historical controls, we will implement several sensitivity analyses that are described in the Table below. These methods were successfully implemented in analysis of our preliminary data.

Table 2. Statistical Approaches	
Question to be Evaluated in Sensitivity Analysis	**Statistical Approach**
For each patient who was eventually treated, if we obtain their average of their AGS scale values prior to treatment (pre-treatment average) and the average of their AGS scale values after treatment (post-treatment average), are the post-treatment averages higher than the pre-treatment averages?	Compute the average of the within subject changes (post-treatment average minus pre-treatment average) with 95% CI; apply the paired t-test to compare the mean of pre-treatment to the mean of post-treatment averages within patients.
Is the average AGS scale value higher after treatment than before treatment, when we modify the previous analysis to include patients who were never treated, by calculating their pre-treatment average AGS scale as the average of all of their AGS scale values?	GEE analysis in which patients who were treated contribute two measurements (pre-treatment average and post-treatment average), while patients who were never treated contribute one measurement ("pre-treatment" average of AGS scale). The GEE model will include an indicator variable for post-treatment and use an exchangeable correlation structure to account for the intra-subject correlation of measurements on each patient.
Does the AGS scale at screening differ from the final value within patients?	Paired t-tests or non parametrics Wilcoxon signed-rank test will be applied as appropriate to compare the screening and final values within patients.

6.3.3.2 Analysis of the GMFM-88

In addition, we will perform a secondary analysis of the GMFM-88 based on the cohort designation in AGS subjects based on their baseline AGS scale. As described earlier, the AGS scale is simple enough to be able to be applied retrospectively, based on clinical notes; this allowed us to develop a historical control cohort for comparison. Based on our pilot data, we have defined three cohorts for this study (Table 3) according to baseline neurologic function as measured by the AGS scale. The more severely affected individuals, due to floor effect, will use the AGS scale as a primary

outcome measure. Individuals with baseline AGS scales of ≥9 have measurable function on the GMFM-88 and other functional assessments and this can be applied to this population.

Changes in GMFM-88 will first be compared between AGS cohorts descriptively, including graphical displays (e.g. overlaid lowess curves for each outcome versus treatment day, by cohort). GEE models will be fitted that model change in outcome over time; these models will include indicator variables for cohorts B and C (with cohort A as reference) and time by cohort interaction terms. Different parameterizations of time will be considered and the fit of models will be compared using goodness of fit criteria for GEE.

Table 3. Cohort designation in AGS subjects based on baseline AGS scale.

AGS cohort
A. AGS scale 0-3
B. AGS scale 4-8
C. AGS scale 9-11

6.3.3.3 Analysis of the ISG scores

Initial analyses will be descriptive (see section 6.3.1). GEE and QLS models will also be fitted, using the same approaches that were described for AGS scale (see sections 6.3.2 and 6.3.3.1). In addition, quantile regression may be applied to evaluate change in median ISG.

6.3.3.4 Analysis of symptoms diaries scores

Initial analyses will be descriptive (see section 6.3.1). GEE and QLS models will be fitted for evaluation of symptoms diaries scores, using the same approaches that were described for AGS scale (see sections 6.3.2 and 6.3.3.1) but potentially with some adjustment for differential timing of measurement.

6.3.3.5 Correlation of within participant changes in primary and secondary outcomes

In addition to individual analysis of each primary and secondary outcome, we will also evaluate the correlation of intra-subject changes in outcomes with Pearson or Spearman correlations, as appropriate. We hypothesize that as the inflammation is lowered (as shown by the IFN score decreasing), the clinical measures of inflammation will improve, as measured by the primary (AGS development score) and secondary outcomes (clinical diaries, GMFM-88).

6.3.3.6 Special considerations

As described earlier, subjects enrolled in the Compassionate Use Treatment Protocol I4V-MC-JAGA (JAGA Compassionate Use study, CHOP IRB Study #13205) for whom commercial supply is not available, will be reconsented to the investigator-initiated JAK inhibitor treatment in AGS study. Data collected as part of their participation in IRB #13205 will be included as part of their longitudinal analysis, including baseline studies. Additionally, subjects who did not transition to this investigator-initiated study because they obtained commercial supply or discontinued participation in I4V-MC-JAGA will be consented via a separate consent form to permit inclusion of their data. For subjects who are considered lost to follow-up (unable to be reached after multiple attempts), a waiver of consent and HIPAA authorization will apply for inclusion of their data. This comprehensive approach is important to overall understanding of efficacy and safety in this ultra rare disease.
Because the JAGA Compassionate Use study protocol and this protocol are carefully aligned, we do not anticipate that any observed within patient changes in study outcomes will be due to differences in procedures between the two studies. However, we will perform sensitivity analyses, to determine if changes in outcomes with treatment differ between the two groups (data from patients enrolled only in the JAGA Compassionate Use study, data from patients who have been enrolled in both the JAGA study and the investigator-initiated JAK inhibitor in AGS study versus data from patients who are solely enrolled in the JAK inhibitor in AGS study). To the GEE model that includes time within patients, an indicator variable for treatment and a time by treatment interaction term, we will add an indicator variable for JAK inhibitor in AGS study and a three way interaction term that is constructed as the product of time and treatment and the study indicator. If the three way interaction term is significant, this will indicate that the impact of treatment (change over time with treatment) differs significantly between groups.

6.3.4 Pharmacokinetic Analysis

Pharmacokinetic sampling may be performed according to the study schedule and analysis may be performed at a later time.

6.3.5 Safety Analysis

All subjects entered into the study at Visit 1 will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs (if any) will be described in detail. AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals**.**

6.4 Sample Size and Power

Sample size calculations were performed using PASS 16 sample size software and were based on preliminary data in 35 patients with available data on the AGS scale.

Analysis of the primary outcome, safety data including laboratory studies and adverse events, will be descriptive and include all individuals, available studies and AEs. Power

analysis is not possible for these analyses, since adverse events may be rare, even in the AGS population, and statistical comparisons may not be feasible.

We anticipate that we will have an evaluable sample size of ~45 treated patients. For the analysis of secondary outcomes, in our preliminary analysis when we compared the average of AGS scales prior to treatment (pre-treatment average) to the average of the AGS scale after treatment (post-treatment average), we observed that the average of within subject changes (post-treatment average minus pre-treatment average) was 0.80 (95% CI = 0.45, 1.16) and that the standard deviation of changes was 1.04. This corresponds to an effect-size of 0.80/1.04 = 0.77. From PASS 16, a sample size of 30 data pairs achieves 98.3% power to reject the null hypothesis of zero effect size when the population effect size is 0.77 and the significance level (alpha) is 0.050 using a two-sided paired t-test. Should the effect-size be smaller than we observed in our preliminary data, we will have 80% power to detect an effect size of 0.53, which would correspond to an average of within subject changes of 0.55, if the SD of changes is 1.04. We will therefore have sufficient power to detect differences that are similar to those observed in preliminary data. For the more complex analyses that are proposed for the larger data set that contains the historical controls (>50), our power will be even greater.

Drop-Out: Overall, this clinical study may enroll up to 55 patients. However, power analysis suggest that an enrollment number of up to approximately 30 is required to obtain results for efficacy that are clinically meaningful, and accounting for those subjects who are found to be ineligible at screening, subjects withdrawn from participation for various reasons and those who are enrolled to this study who are not initially eligible at screening. In addition, some participants may be lost to follow up, or may not survive until one-year post-baseline, when the primary efficacy analysis will be conducted. Thus, we expect to be able to perform the necessary analysis even if there is significant drop out.
We will evaluate the reasons for drop-out carefully, especially with respect to the missing at random assumption that is required for GEE/QLS regression. As described above, a sample size of 30 patients will be adequate for analysis of our primary outcome. The goal of the secondary analyses will be primarily to inform the generation of hypotheses for future studies in this population.
The analysis of data obtained from this group of initially ineligible, but prospectively approved subjects entered to the study, will be assessed independently of the main group of subjects who meet all eligibility criteria. The statistical analysis within this group will depend on the total number of subjects in the group, as well as the degree of clinical heterogeneity of these patients. If the sample size is large enough we will attempt to replicate the analyses that are performed for the eligible participants in this group.

7 STUDY MEDICATION (STUDY DEVICE OR OTHER STUDY INTERVENTION)

7.1 Description

7.1.1 Packaging

Baricitinib will be dispensed by the investigational pharmacy in labeled containers.

7.1.2 Labeling

Individual labeling for drug packaging will be provided by the investigational pharmacy.

7.1.3 Dosing

Baricitinib can be taken orally or administered via G-tube. Baricitinib should be handled with gloves by caretakers. Dosing will be performed according to dosing tables (Appendices 3 and 4).

7.1.4 Treatment Compliance and Adherence

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.

7.1.5 Drug Accountability

Adequate records of study drug receipt and disposition will be maintained by the CHOP Pharmacy. Records of receipts, investigational drug orders, dispensing records, and disposition forms will be examined during the course of the study. The purpose of these records is to ensure regulatory authorities that the investigational new drug will not be distributed to any person who is not a study subject under the terms and conditions set forth in this protocol. The study medication is to be prescribed by the Investigator or designee and may not be used for any purpose other than that described in this protocol.

8 SAFETY MANAGEMENT

The study protocol will be submitted to the FDA and will be reviewed by the study DSMB and the Medical Monitor. Participant enrollment may only begin after final IRB approval and FDA authorization to proceed.

8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

8.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) 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.

8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.
As defined in title 21 of the Code of Federal Regulations Part 312, an *adverse event (AE)* is “any untoward medical occurrence associated with the use of a drug, whether or not considered drug related”. All adverse events will be classified using the current version of Common Terminology Criteria for Adverse Events (CTCAE), developed and maintained by CTEP at the National Cancer Institute.
A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "reasonable possibility" means that there is evidence, such as a temporal relationship, to suggest a causal relationship between administration of drug and the adverse events. It is less certain about causality than *adverse reaction*.

8.4 Definition of a Serious Adverse Event (SAE)

Title 21 of the CFR also provides a definition for serious adverse events (SAEs), described as those events that result in death; or are life-threatening; or require prolonged inpatient hospitalization or prolongation of existing hospitalization; or create persistent or significant disability/incapacity, or a congenital anomaly/birth defects. However, application of this definition is difficult in subjects who, as a result of their

underlying congenital disorder, present with life-threatening illness. Therefore, for this study, we modify the standard definition, and define **serious adverse events** as those events that**:**

- Result in death.
- Are life-threatening, that is, places the patient at immediate risk of death from the event as it occurred.
- Require hospitalization.
- 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.

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. Elective admissions for surgeries or interventions, such as orthopedic surgeries, that are expected complications of AGS, will not be considered SAEs. Admissions for expected complications of AGS, including seizures, changes in neurologic function, interventions for tone management, interventions for feeding failure, will not be considered SAEs. All admissions associated with infection or hematologic disturbances will be reported as SAEs.

8.4.1 Expected and Unexpected Adverse Events

An unexpected adverse event or reaction is defined as any adverse experience, the specificity or severity of which is not consistent with the risks of information described in the protocol. Expected adverse events are those that are identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participation in the study or are part of the clinical spectrum of the underlying disorder. Common acute and chronic complications of AGS include but are not limited to:

- Seizures
- Intermittent encephalopathy
- Progressive decline in neurologic function
- Skin rashes (such as chilblains) including panniculitis and secondary infections and amputations
- Large vessel central nervous system vasculitis
- Lupus like renal dysfunction
- Autoimmune hepatitis and elevation of liver enzymes and liver function tests
- Pulmonary hypertension
- Cardiomyopathy
- Myopathy
- Glaucoma
- Gastrointestinal disease with bowel inflammation
- Urinary tract infection
- Hip dislocation or scoliosis

- Chronic lung disease
- Spasticity and dystonia
- Feeding difficulties
- Thrombocytopenia
- Anemia
- Hypothyroidism
- Gastroesophageal reflux

8.4.2 Relationship of SAE to study drug or other intervention

Relationship of study drug to the adverse event or suspected adverse reaction is defined as follows:

- Unrelated: Adverse event is clearly due to extraneous causes (e.g., underlying disease)

- Unlikely related (must have 2 of the below):
  - Does not have temporal relationship to drug administration
  - Could readily have occurred due to subject's clinical state
  - Could have been due to environment or other interventions
  - Does not follow known pattern of response to drugs
  - Does not reappear or worsen with reintroduction of drug

- Possibly related (must have 2 of below):
  - Drug administration and the occurrence of the AE are reasonably related in time
  - Could not readily have occurred due to subject's clinical state
  - Could not readily be due to environment or other interventions
  - Follows a known pattern of response to drug

- Probably related (must have 3 of the below):
  - Drug administration and the occurrence of the AE are reasonably related in time
  - Could not readily have occurred due to subject's clinical state
  - Could not readily be due to environment or other interventions
  - Follows a known pattern of response to drug

- Definitely related (must have all 4 of the below):
  - Drug administration and the occurrence of the AE are reasonably related in time
  - Could not readily have occurred due to subject's clinical state
  - Could not readily be due to environment or other interventions
  - Follows a known pattern of response to drug

8.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The study coordinator is responsible for collecting and recording all clinical and laboratory data. Adverse events will be collected on subjects at all follow ups, as well as by phone or e-mail communication with parents 4 weeks following initiation of study agent. The reporting period for new AEs is the period from the start of study drug administration until one month after cessation. Follow-up reports on AEs should continue up to 30 days after the administration of drug if the AE did not resolve.
For each AE, the site investigator will assess severity, and whether the event meets the definition of a serious adverse event and will report whether baricitinib treatment was interrupted or stopped, as well as the outcome of the AE. If the event is an SAE, both the site PI and the Medical Monitor will assess the relationship to drug.
If a non-serious adverse event is unresolved at the time of assessment, the site investigator will make a clinical assessment as to whether continued follow-up of the AE is warranted, and the results of this assessment must be documented. If a non-serious adverse event is unresolved at the time of discharge from the study, the Principal Investigator and the Medical Monitor will make a joint clinical assessment as to whether continued follow-up of the AE is warranted. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.
The PI will prepare aggregate reports of all adverse events (serious/not serious and expected, unexpected) for the DSMB and the IRB as required and for the FDA on an annual basis.
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.

8.5.1 Reporting of Serious Adverse Events

Serious adverse events (SAEs) that are either life-threatening or which result in death must be reported by the PI to the IRB and the Medical Monitor via telephone, fax or email within one business day of discovery. The full report must be submitted to the IRB within 48 hours of initial notification. The Medical Monitor (or their delegate) will then be contacted by the PI and be informed of the details of the SAE, to determine if it meets the reporting requirement of a serious and unexpected suspected adverse reaction. Investigators are required to submit follow-up reports to the initial report as promptly as is feasible. The PI will submit a report of the SAE to the FDA within 15 calendar days of the event, if the event meets the reporting requirement of a serious and unexpected suspected adverse reaction. In those cases, the PI will also report the event to the DSMB. In all other cases, the PI will submit the report as part of periodic reporting to the DSMB and FDA.
Events that are not life-threatening and do not result in death must reported to the IRB within 7 business days of discovery.
The Medical Monitor will review causality (unrelated, not likely related, possibly related, probably related, definitely related) of the serious adverse event. The Medical Monitor

may request further information if necessary and possibly request changes to the protocol or consent form as a consequence of the adverse event.
Additionally, the PI will be responsible for reporting SAEs to the IRB within the time mandated by this IRB. The PI will inform all investigators of any safety updates or changes.
SAEs occurring after a patient has taken the last dose of investigational product will be collected in 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 assesses the events were related to either investigational product, or a study procedure, and unexpected.

8.5.2 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Prescribing Information and that the investigator identifies as related to investigational product or procedure.

8.5.3 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.6 Notifications of SAEs/IND Safety Reports to the FDA

Unexpected fatal or life-threatening adverse events that are related to the study drug, will be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.
Unexpected serious adverse events that are related to the study drug but not fatal or life-threatening, will be reported to FDA as soon as possible but no later than within 15 calendar days following the sponsor's initial receipt of the information.
Follow-up reporting: Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report will be submitted as a Follow-up IND Safety Report. Such report will be submitted as soon as the information is available, but no later than 15 calendar days after the sponsor receives the information.

8.7 Study Stopping Rules

There are some circumstances which potentially may arise, requiring temporary study stop. A serious adverse event, directly related to the use of study drug, will prompt a temporary stop to discuss the event with the DSMB and FDA. The IRB will be notified in accordance with CHOP IRB SOP 408. The study will proceed only with documented concurrence of the DSMB, FDA and the IRB, as applicable.

The occurrence of two non-fatal SAEs directly related to use of the study drug or one death directly attributed to use of the study drug will stop the study.

8.8 Safety Management and Monitoring Guidance

The following Appendices should be followed. Appendices 9-12 in particular serve as guidance for management of abnormal laboratory values identified during screening or safety follow-up of enrolled individuals.

Study schedule, Overall	Appendix 1
Study Timeline	Appendix 2
Dose Escalation Schedule for Patients with eGFR ≥60 mL/min/1.73 m2 or Normal eGFR for Age <24 Months	Appendix 3
Dose Escalation Schedule for Patients with eGFR 30 - <60 mL/min/1.73 m2 or for Age <24 Months with abnormal eGFR	Appendix 4
AGS severity scale	Appendix 5
Patient Daily Diary for AGS infants 0-6 months	Appendix 6
Patient Daily Diary for AGS > 6 months	Appendix 7
Clinical Laboratory Tests	Appendix 8
Management of Liver Enzyme Laboratory Values	Appendix 9
Management of Leukocyte associated laboratory testing and IgG	Appendix 10
Management of Anemia	Appendix 11
Management of Thrombocytopenia and Thrombocytosis	Appendix 12
Cutaneous LE Disease Area and Severity Index (CLASI)	Appendix 13
Dose tapering guidance	Appendix 14
Decision tree in case of infection suspicion or confirmation	Appendix 15
Concomitant medication approach in patients with AGS receiving baricitinib	Appendix 16

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

There are no randomization procedures.

9.1.2 Blinding

There are no blinding procedures.

9.1.3 Unblinding

There are no unblinding procedures.

9.2 Data Collection and Management

9.2.1 REDCap for Study Data Management

The study will utilize REDCap to provide a Web-based data collection, data management system. REDCap is an NIH-supported, broadly-used tool developed and continually improved by Vanderbilt University. CHOP has had very substantial experience in the implementation and support of REDCap data bases for clinical trials. Specifically, Dr. Vanderver already has in place a REDCap database designed specifically for AGS. Database fields correspond to expected disease complications and anticipated possible adverse outcomes. CHOP provides support for the management and curating of datasets from REDCap. Especially important are reports to the Data and Safety Monitoring Board (DSMB) charged with ensuring the safety of study participants. Finally, the database is directly accessible to standard statistical packages such as SAS, SPSS, and STATA so that interim and final analyses can be conducted without the need to transport data. REDCap reports will monitor recruitment overall. It will warn of recruitment problems by plotting actual vs. expected screens, recruits and enrollees.

9.2.2 Additional Study Data Management

The study will also utilize OnCore Clinical Trials Management System and Advarra EDC, CHOP Research IS secured electronic data capture systems, which will be used for study scheduling, data collection and analysis (e.g. eCRFs), as well as billing and regulatory purposes. OnCore Clinical Trials Management System and Advarra EDC are secure electronic data capture systems with access controls and a data backup plan. The systems are password protected. Only study team members will have access to study documents, subject data and case report forms stored in these systems. Access to the systems is monitored and logged for review if needed.

9.2.3 Data Security

There are several layers of security that protect the data stored in REDCap and OnCore. The first layer consists of network security, through firewalls, and is designed to limit access to authorized users and to deny access to all others. The firewall blocks malware and prevents flooding. The second layer consists of database authentication. This limits access to the database to those individuals passing layer one who have an assigned database account and can enter the correct, suitably complex, user-defined password for that account. The third layer consists of controlling a user's capabilities, what a user can see and do, based on the user's role in each investigation. Each user needing access to the data for a study must be included on the list of key staff for that specific study in the protocol and must be assigned a study role. If a user is not in the key staff list of the study s/he will not be granted access to that study's data even if s/he has a valid password associated with another study. Key staff will only be allowed to perform those tasks that are dictated by the person's defined role in the study. For instance, a person who enters data will only be able to add records to specific data files; s/he cannot peruse or make changes to existing records in the database. Only those persons who have clinical responsibilities for the patient would be able to see patient identifying information. There is provision for the PI to be able to over-ride, to widen or narrow, the capabilities assigned based on study role.

Lastly, to protect patient confidentiality, study research data is coded and separated from all patient identifying information. The confidential data is stored separately and the information is encrypted to offer additional protection. Each research participant in a study is assigned an anonymous participant ID number that can be used to link together a participant's de-identified research records but not to link directly to the confidential identifying data. Since there must be a way to link to that data to identify patients for scheduling and mailings, etc., a second arbitrary number called a universal identifier is assigned to each participant's confidential data record. That number is linked to the participant ID via a second translation file that is also encrypted. Therefore, in the extremely unlikely event that an unauthorized person gained access to the confidential data file all s/he would see is gibberish without having the appropriate key to decrypt the data. Likewise, all transmissions to and from REDCap are sent using secure HTTP (HTTPS), which encrypts all transmissions so that even if they were intercepted their content would be unreadable by all but the intended recipient.

There are also two other components to security and they are monitoring and system administration. The network is closely monitored and all activity is logged. Both the real time monitor and the logs are reviewed by eye and by computer to identify suspicious activity so that it can be dealt with appropriately. Furthermore, all access to research data is audited and all activities are logged so that if a problem occurs it will be possible to identify who was responsible and how it happened. The system and database software are kept up-to-date with the latest security protections released for the operating system and for the database. These measures help us to keep ahead of the threats to security or to close loopholes before they can be more widely exploited. Finally, there is excellent physical security; access to the systems is key pad controlled, there is a backup generator to provide power to keep systems operating in the event of

power failure, all computer rooms housing database and web servers are environmentally-controlled and protected against flood and fire.

9.2.4 Data Acquisition and Entry

Data collection for this study will be accomplished with online electronic case report forms.

- On-line forms will be developed that contain the requisite data fields.
- For each subject enrolled all study-related visits of the enrollment, diagnostic, application, observation, termination and follow-up phases will be recorded in the CRF. This CRF must be completed and signed by the investigator for every subject on whose behalf written informed consent was given. This also applies to subjects who fail to complete the study. If a subject is being withdrawn from the study by his/her parent(s)/legal guardian(s), the reason must be stated in the CRF, if the parent(s)/legal guardian(s) are willing to provide such reason. If a subject is withdrawn from the study because of a limiting AE, reasonable efforts should be made to clearly document the outcome.
- All subjects will be identified by their subject number.
- Each investigator will be responsible for ensuring that the identification of his/her subjects is possible at any time.
- The investigator will use CRF Completion Guidelines to ensure that data is complete and accurate. These guidelines will provide instructions on how to complete, correct, and archive final copies of the CRFs.
- Prior to the beginning of the study, the investigator must establish a list of the individuals with trial related duties and of the persons authorized to make entries and data changes in the CRFs.
- These persons will be listed, including details on their function in the study, their full names, initials, and signatures, and the date of their assignment to (and, if applicable, their demission from) their respective duties on this study, on the center sample signature page in the investigator's file.

9.2.5 Data Editing

A number of data checks and procedures may be applied during data collection that either prevent errors or detect them with the requirement for later review and adjudication. No matter what the data source all data must pass through all predefined data checks and all potential errors must be reviewed and corrected or accepted with comment. Any discrepancies are reported in a data exception feedback report for correction and are monitored to ensure that they are accepted or corrected. Predefined procedures and data checks include:

- choosing forms and participants for data entry from the list of predefined enrollees avoiding the errors that can occur when ID numbers are entered directly on forms;
- implementing validation and consistency checks before data are sent to the database to allow correction but logging of all uncorrected exceptions for required later review; and

- checking for and recording on each form the rate of missing data that can be used to set criteria for subsequent forms processing, e.g. to reject forms with high missing data rates from entering the database; and
- flag out of range values
- creating a context sensitive comment window that allows subsequently retrievable text to be linked to any form or data item, e.g., to explain an unusual data response.

Web-based, forms allow data to be viewed and edited. Quality assurance checks are applied during data entry and editing. In addition to maintaining a time-stamped audit trail of all logins and transactions, the system has the capability to be proactive, for example in requiring all unflagged data corrections be accompanied by a justification as well as to be adjudicated, reviewed, accepted or rejected, by a designee. Together these options and procedures promote a high degree of completeness, and accuracy of study data.

9.2.6 Data Entry Training

Data entry training will be conducted on line using the REDCap database and OnCore and Advarra databases. Study coordinators will be trained and certified in on-line use of the REDCap and OnCore databases. Training sessions will be scheduled and organized by members of the study team.

9.2.7 Data Quality Assessment (QA)

Data quality is assessed at the data entry point using intelligent review and controls during on-line data entry or edits via study forms. QA reports assess data quality post-data entry. Data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Equally important quality assurance measures are the internal checks for reasonableness and consistency that will be implemented via simple tabulations and cross tabulations that should reveal any remaining data quality issues.

9.3 Confidentiality

By conducting this study, the investigator pledges that he/she will keep all information pertaining to the study strictly confidential, including data generated from this study, except as exempted for regulatory purposes.
Blood and urine samples will be collected and diagnostic records will be reviewed. Data recorded will include demographics, clinical summary, diagnostic tests and study results. All research data, including identifiers, will be accessible only to the research team and as required by law.

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

A DSMB has been assembled by the investigators. This Board is responsible for safety and accuracy monitoring of the data entered by the investigators. The DSMB will regularly evaluate trial performance, monitor interim data for safety and effectiveness of study regimens, review any protocol modifications, and advise the investigators

regarding early termination or continuation of a study based on the interim monitoring or scientific findings. The DSMB will receive and respond to reports of any serious adverse events (SAEs) and will be immediately notified of fatal or life-threatening events. Based on the review of safety, efficacy, and performance data, the DSMB will make recommendations regarding conduct of the study. It is expected that the DSMB will meet as per the DSMB Charter.

9.4.2 Risk Assessment

9.4.2.1 Risks associated with Baricitinib

Baricitinib is Janus Kinase inhibitor which blocks the intracellular signaling response of interferon by limiting downstream activation of the interferon receptor. Janus Kinase inhibitors, including baricitinib, may therefore have risks associated with infection, as well as other serious risks. These are detailed below, and further information is available in prescribing information.

9.4.2.1.1 Serious Infections and Viral Reactivation

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in rheumatoid arthritis patients receiving baricitinib. The most common serious infections reported with baricitinib included pneumonia, herpes zoster, and urinary tract infection (see Adverse Reactions).

Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, esophageal candidiasis, pneumocystosis, acute histoplasmosis, cryptococcosis, cytomegalovirus, and BK virus were reported with baricitinib. Some patients have presented with disseminated rather than localized disease and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids.

As of March 2020, fungal pneumonia was reported in a single AGS patient receiving baricitinib and also receiving concomitant therapy with corticosteroids during the Lilly expanded access program. Vigilance for infections should remain high in particular in children with any concomitant medications increasing immunosuppression, or hematologic parameters suggestive of immunosuppression.

Prophylaxis for serious infections will be recommended based on CD4, IgG, ANC and ALC levels as per section 4.6.

To minimize these risks, screening includes careful assessment of infections prior to drug initiation, including HIV, hepatitis, tuberculosis, HSV, CMV, EBV, and BK virus. In addition, ongoing evaluations, including clinical assessments for infection, and laboratory testing for HSV (IgG/IgM), CMV PCR, EBV PCR and tuberculosis (via quantiferon gold testing, only for patient in endemic regions) during treatment, will be conducted as clinically indicated.

Patients will be monitored for BK viremia at baseline, and every six months until they reach two years of age. Over two years of age, complete follow-up BK testing will be performed if any of the following is observed: blood in urine not explained by a urinary

tract infection (as defined by greater than 10 RBCS in HPF), equal to or greater than 1+ protein on a first morning urine sample not explained by a urinary tract infection (positive), decrease in eGFR (30 - <60 mL/min/1.73 m^2).

Children with AGS are at risk of respiratory, skin and urinary tract infections as part of their disease. Unless these infections fall into the categories below, there will not be drug discontinuation for these events. Patients will receive treatment as clinically indicated for these infections. Discontinuation of baricitinib has been associated with neurologic decline in patients with AGS[17], leading to greater caution around holidays from drug therapy in the context of acute infections.

Certain categories of infections will require specific management:

Serious infections are defined as those resulting in or occurring during hospitalization, or need for parenteral antimicrobial treatment. In these cases, the diagnostics and treatment plan will be discussed with local infectious disease team for decisions regarding continuation, decrease or interruption of study treatment. All events where infection is associated with hospitalization or need for parenteral antimicrobial treatment will be reported to the DSMB and IRB as a SAE within 24 hours of learning of the event. Patients will receive treatment as clinically indicated regardless of treatment decisions for baricitinib.

Disseminated/complicated herpes zoster, for which drug cessation will occur until improvement in symptomatic herpes zoster infection occurs (resolution of PCR positive serologies or all lesions crusted) as confirmed by local infectious disease team. Disseminated/complicated herpes zoster is defined as multidermatomal involvement in cases of reactivation, central nervous system involvement or systemic involvement including hepatitis or pneumonitis). After improvement, baricitinib may be resumed. Herpes zoster that is not confirmed, is self resolving, limited to skin without CNS, hepatic or pulmonary involvement, will result in discussion with local infectious disease team but will not result in immediate drug discontinuation. The infection will be managed as clinically indicated. Patients will receive treatment as clinically indicated regardless of treatment decisions for baricitinib. All events of disseminated/complicated herpes zoster will be reported to the DSMB and IRB within 24 hours of learning of the event as a reportable event.

Viral reactivation, including EBV/CMV reactivation. In these cases, the diagnostics and treatment plan will be discussed with local infectious disease team for decisions regarding continuation, decrease or interruption of study treatment. Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies with baricitinib. If a patient develops disseminated/complicated herpes zoster, we will interrupt treatment until the episode resolves (i.e. until symptomatic improvement of the herpes zoster occurs). EBV and CMV may also be reactivated during treatment, and both EBV and CMV will be monitored during study safety laboratory testing (via PCR) if hematologic or hepatologic parameters suggest infection. If a patient develops clinically relevant reactivation, we will notify local infectious disease team to establish whether to continue, decrease or interrupt treatment until improvement is seen in viral titers or organ involvement (see Appendix 15). All events of EBV/CMV reactivation will be reported to the DSMB and IRB

within 7 days of learning of the event as a reportable event. Patients will receive treatment as clinically indicated regardless of treatment decisions for baricitinib.

Infections occurring in cases where ANC, ALC, IgG, CD4 are at levels that need additional monitoring as defined in the protocol. In these cases, the diagnostics and treatment plan will be discussed with local infectious disease team for decisions regarding continuation, decrease or interruption of study treatment. All events will be reported to the DSMB and IRB within 7 days of learning of the event as a reportable event. Patients will receive treatment as clinically indicated for these infections regardless of treatment decisions for baricitinib.
Appendix 15 details a decision tree in case of suspicion or confirmation of infection.

9.4.2.1.2 Tuberculosis

Patients will be evaluated for latent or active infection prior to administration of baricitinib. Baricitinib should not be given to patients with active TB. We will consider anti-TB therapy prior to initiation of baricitinib in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Table 4: Adverse Reactions occurring in greater than or equal to 1% of Baricitinib 2 mg and Baricitinib 4 mg Treated Patients in Placebo-Controlled Trials

Events	Weeks 0-16		
	Placebo n=1070 (%)	Baricitinib, 2 mg n=479(%)	Baricitinib 4 mg n=997 (%)
Upper respiratory tract infections[a]	11.7	16.3	14.7
Nausea	1.6	2.7	2.8
Herpes simplex[b]	0.7	0.8	1.8
Herpes zoster	0.4	1.0	1.4

a. Includes acute sinusitis, acute tonsillitis, chronic tonsillitis, epiglottitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinobronchitis, sinusitis, tonsillitis, tracheitis, and upper respiratory tract infection.
b Includes eczema herpeticum, genital herpes, herpes simplex, ophthalmic herpes simplex, and oral herpes.
Additional adverse drug reactions occurring in fewer than 1% of patients: acne

9.4.2.1.4 Malignancy and Lymphoproliferative disorders

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with baricitinib. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

9.4.2.1.5 Thrombosis

Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), has been observed at an increased incidence in adult patients treated with baricitinib compared to placebo. In addition, arterial thrombosis events in the extremities have been reported in clinical studies with baricitinib. Many of these adverse events were

serious and some resulted in death. There was no clear relationship between platelet count elevations and thrombotic events. As of March 2020, in one patient with AGS, thrombosis of the pulmonary vasculature, associated with previously unrecognized severe pulmonary hypertension, caused death. Thus, baricitinib should be used with caution in patients who may be at increased risk of thrombosis, and in particular in AGS patients with underlying pulmonary hypertension. In AGS, regular screenings for pulmonary hypertension will occur according to clinical recommendations. If clinical features of DVT/PE or arterial thrombosis occur, patients should be evaluated promptly and treated appropriately.

9.4.2.1.6 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical studies with baricitinib, although the role of JAK inhibition in these events is not known. Baricitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

9.4.2.1.7 Bone growth

During a juvenile rat study completed to support the dosing of baricitinib to patients 1 to <12 years, there were reductions in overall growth evidenced by lower body weights. Additional skeletal effects were observed in the juvenile rat study including marginal-to slight decreases in femur and tibia size as well as an apparent acceleration of normal maturation ossification centers. These findings were not associated with premature closure of growth plates or other functional consequences. Microscopically, there was a focal increase in trabecular bone. The effects of baricitinib in the pediatric population is not characterized. In addition, it should be noted that children with AGS have decreased overall growth which is assumed to be related to their chronic inflammatory disease.

9.4.2.2 Laboratory Abnormalities

9.4.2.2.1 Neutropenia

Treatment with baricitinib was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm^3) compared to placebo. CBC will be checked in individuals with ongoing treatment with baricitinib according to the study schedule and management of laboratory abnormalities will be performed according to Appendix 10. We will avoid initiation, decrease (Appendix 14) or interrupt baricitinib treatment in patients according to Appendix 10. Discussion with the study staff included in the Dysregulated Immune Response Team will help to determine if this complication is caused by AGS (see Appendix 10 for guidance). Testing will be performed as detailed in Appendix 10 and prophylaxis for individuals with abnormal values will be implemented as discussed in this section.

9.4.2.2.2 Lymphopenia

ALC less than 500 cells/mm^3 were reported in baricitinib clinical trials. Lymphocyte

counts less than the lower limit of normal were associated with infection in patients treated with baricitinib, but not placebo. CBC will be checked in individuals with ongoing treatment with baricitinib according to the study schedule and management of laboratory abnormalities will be performed according to Appendix 10. We will avoid initiation, decrease (Appendix 14) or interrupt baricitinib treatment in patients according to Appendix 10. Discussion with the study staff included in the Dysregulated Immune Response Team will help to determine if this complication is caused by AGS (see Appendix 10 for guidance). Testing will be performed as detailed in Appendix 10 and prophylaxis for individuals with abnormal values will be implemented as discussed in this section.

In addition, IgG and lymphocyte subset testing will be performed as detailed in section 4.6 and prophylaxis for individuals with abnormal values will be implemented as discussed in Appendix 10.

9.4.2.2.3 Anemia

Decreases in hemoglobin levels to less than 8 g/dL were reported in baricitinib clinical trials. CBC will be checked in individuals with ongoing treatment with baricitinib according to the study schedule and management of laboratory abnormalities will be performed according to Appendix 11. We will avoid initiation, decrease (Appendix 14) or interrupt baricitinib treatment in patients according to Appendix 11. Discussion with the study staff included in the Dysregulated Immune Response Team will help to determine if this complication is caused by AGS (see Appendix 11 for guidance). Testing will be performed as detailed in Appendix 11 and prophylaxis for individuals with abnormal values will be implemented as discussed in this section.

9.4.2.2.4 Liver Enzyme Elevations

Treatment with baricitinib was associated with increased incidence of liver enzyme elevation compared to placebo. Increases to greater than or equal to 5x and greater than or equal to 10x upper limit of normal (ULN) were observed for both ALT and AST in adult patients in baricitinib clinical trials. Additionally, without treatment, increases of both ALT and AST are seen in one-third of individuals affected by AGS. Liver function and enzyme testing will be checked in individuals with ongoing treatment with baricitinib according to the study schedule and management of laboratory abnormalities will be performed according to Appendix 9. Discussion with the study staff will help to determine if this complication is caused by AGS (see Appendix 9 for guidance).

9.4.2.2.5 Lipid Elevations

Treatment with baricitinib was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol in adult patients. Lipid parameters will be checked in individuals with ongoing treatment with baricitinib according to the study schedule. We will manage patients according to clinical guidelines for the management of hyperlipidemia and with the assistance of study staff.

The following guidelines will be considered:

- If TG >400, repeat fasting sample. If still elevated >400, refer to a provider with experience in lipid management.
- If LDL>160, refer to a provider with experience in lipid management.
- If HDL<25, refer to a provider with experience in lipid management.

9.4.2.3 Vaccinations

We will avoid use of live vaccines in patients undergoing treatment with baricitinib. Infants who should receive live vaccines during the period of baricitinib treatment will be counseled by a physician other than the investigators (e.g. Medical Monitor) on the relative risks of vaccination versus treatment without vaccination. Whenever medically safe, we will update immunizations in agreement with current immunization guidelines prior to initiating baricitinib therapy. Patients will not be treated earlier than 4 weeks after receiving live vaccines with the exception of the oral rotavirus vaccination, for which patients will not be treated earlier than 2 weeks after receiving vaccination, and the Typhoid and BCG vaccine which will require 12 weeks after vaccination prior to receiving baricitinib.

9.4.2.4 Risks associated with Blood Testing

Needle punctures for blood draws may cause some pain, bleeding or bruising and rarely, may cause fainting or infection**.** This risk is similar to the risk encountered by affected patients during routine clinical care.

9.4.2.5 Risks of Physical Exam including functional assessments

There are no physical risks associated with a physical exam or functional assessments but it may cause momentary embarrassment or discomfort. This risk is similar to the risk encountered by affected patients during routine clinical care.

9.4.2.6 Risk of Interview/Questionnaires including functional assessments

There are no physical risks associated with questionnaires or functional assessments but it may cause momentary embarrassment or discomfort. This risk is similar to the risk encountered by affected patients during routine clinical care.

9.4.2.7 Breach of Privacy and Confidentiality

As with any study involving collection of data, there is the possibility of breach of confidentiality of data. Every precaution will be taken to secure participants' personal information to ensure confidentiality. At the time of participation, each participant will be assigned a research program identification number. This number will be used on data collection forms, blood samples, and in the database instead of names and other private

information. A separate list will be maintained that will link each participant's name to the research program identification number for future reference and communication.

9.5 Benefits

9.5.1 Potential Benefits of Trial Participation

Based on existing preliminary data (see introduction) it is expected that some patients will benefit from trial participation. Benefits may include control of systemic features including improvement of abnormal liver and hematologic parameters, improved comfort, improvement in skin manifestations and in some cases, improved neurologic function.

9.5.2 Risk-Benefit Assessment

Based on existing preliminary data (see introduction) the Risk-Benefit assessment justifies proceeding with providing baricitinib in a clinical trial setting to individuals affected by AGS. Baricitinib has been generally well tolerated with improvement in measures of comfort and skin involvement, with additional neurologic benefit in a subset of affected individuals.
Additionally, study staff will make every effort to limit other risks associated with study participation including the following measures:

- The drug will be handled by the respective site investigational drug pharmacy and will be dispensed by that pharmacy.
- The participants and their families will be provided psychological and emotional support to deal with the results of the diagnostic testing.
- Confidentiality is protected to the full extent required by law and applicable local, State and Federal regulations and guidance including HIPAA.
- All medical records, including case report forms, will be kept in locked files accessible only to the health professionals involved in the clinical research or responsible for the participant’s care, governmental agencies (e.g., FDA, NIH), and local convening authorities (e.g., IRB, DSMB) for the purpose of audit regarding scientific validity and/or aspects pertaining to the ethical conduct of human clinical investigation. Identifier data are not released without the parent’s/participant’s knowledge and consent. Electronic databases with identifier data are user ID/password protected.
- The results of the study will be shared with the participants of the study as soon as they become available.

9.6 Recruitment Strategy

Participants will be recruited by advertisement via testing laboratories, family advocacy organizations, self-referral, or participation in a clinical leukodystrophy program. Patients’ families will be first contacted by non-study personnel to discuss the possibility of participating in a clinical trial. If the patient is also a patient of the investigators, study participation will be discussed with the Medical Monitor. Should the family be interested, patients and families will be invited to contact the investigative team to discuss participation and ICF documents will be shared with the family. Should the family continue to be interested, the family will be invited to visit CHOP. Medical records will be

collected for verification of study eligibility, including mutation status as part of clinical standard and care and not as part of this research, after release of information and after consent for screening (see below).

9.7 Informed Consent/Assent and HIPAA Authorization

During the screening period, telephone consent may be obtained by study staff to facilitate the explanation of the study procedures and screening visit. In all cases, if a telephone consent was obtained during the screening period, written consent will be obtained by the investigator or designee during the enrollment visit.
The investigator or designee will meet with the parent(s) or legally authorized representative to describe the study. Parents will be brought to a private, quiet room where the benefits and risks of the study will be explained thoroughly, and any questions will be answered. The investigator or designee will then give the parent(s) time to read the consent form and consider participation. The investigator or designee will return to answer questions and ensure that the legally authorized representative understands the information provided and obtain informed consent.

For patients transferred from the JAGA Compassionate Use study (CHOP IRB Study #13205), informed consent may occur remotely, by video or phone, if the patients or their parent(s) or legally authorized representative(s) are not able to come on-site. In this case, informed consent documents will be sent by mail, secure email or secure facsimile (from a fax device only accessible to the study team or RightFax, a CHOP-approved fax application) to the legally authorized representative ahead of time, prior to the video of phone visit, to give them time to read the consent form and consider participation. During the phone or video visit, the investigator or designee will answer questions and ensure that the legally authorized representative understands the information provided. If video visits are used, they will be completed on myCHOP, a CHOP-secure system. If the legally authorized representative is willing to participate, they will be asked to sign the consent form at the end of the visit, and to return the signed consent form by mail, secure email or facsimile (to a fax number only accessible to the Study Team), for signature of the investigator or designee. Once the consent form is fully signed, a copy will be provided to the legally authorized representative by mail, secure email or secure facsimile (from a fax device only accessible to the study team or RightFax, a CHOP-approved fax application).

For subjects who did not transition to this investigator-initiated study because they obtained commercial supply or discontinued participation in the JAGA Compassionate Use study (CHOP IRB Study #13205) will be consented via a separate consent form to permit inclusion of their data.

Consent for all patients may also take place via the Part 11 compliant REDCap e-consent feature.

Informed consent documents will be available in English. If the parents are only fluent in another language, and the site has a standard operating procedure for informed consent in that language (such as an on-call interpreter, abbreviated consent form in

English) and the site IRB has approved the process for this study in advance, non-English speaking parents/guardians will also be included.

To obtain consent from patients with Limited English Proficiency (LEP) using the Part 11 compliant REDCap e-consent feature, a Short Form template will be made available in REDCap in the appropriate language. The interpreter/witness who will have attended the consent visit will also be able to sign the consent using the Part 11 compliant REDCap e-consent feature.

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 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 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.
As used in this protocol, the term "informed consent" includes all consent given by a legal representative.

- It is the responsibility of the investigator to ensure that no subject is enrolled in any study-related examination or activity before written informed consent has been obtained.
- Written informed consent will be obtained in compliance with 21 CFR Part 50 and the ethical principles that have their origin in the Declaration of Helsinki.
- The subject's legal representative(s) will be informed that they are completely free to refuse to enter the study or to withdraw from it at any time.
- Subjects whose legal representative(s) refuse to give written informed consent or withdraw their informed consent later on must not be included into the trial or must be excluded from further participation, respectively. Before personally dating and signing the informed consent form, the subject's legal representative(s) will be informed in detail by the investigator or a designee of the investigator about all pertinent aspects of the trial according to 21 CFR Part 50 and ICH GCP.
- The subject's legal representative(s) should be given sufficient time to request further details about the trial before signing the informed consent form, in accordance with the ICH GCP Guidelines (1997).
- The receipt of the informed consent from the legal representative(s) must be documented on the appropriate page of the subject's CRF and in the source documents.
- One copy of the consent form signed and dated by the subject's legal representative(s) and by the physician who informed the legal representative(s) will

be kept at the study site; a second copy will be provided to the subject's legal representative(s).
- Written HIPAA authorization will be obtained from the combined informed consent form.

Potential subjects can also be pre-screened over the phone, in which case patients or their guardians will undergo telephone consent, to explain the purpose and procedure of the study. Formal written consent will be obtained at Visit 1.

9.7.1 Waiver of Consent and HIPAA Authorization

Waivers of consent/parental persmission, assent, and HIPAA authorization are requested for participants previously enrolled in the JAGA Compassionate Use study (CHOP IRB #16-013205) that were lost to follow-up and unable to provide consent for inclusion of their data as discussed in Section 9.7. A subject will be considered lost to follow-up if five (5) attempts (on separate days) to contact the subject by phone or email have been unsuccessful. A waiver of consent and HIPAA authorization is requested for continued use of the existing data.

Inclusion of these patients' data is important for baseline comparison, overall understanding of efficacy and safety in this ultra rare disease and ensuring generalizability of results. Only up to a Limited Data Set will be included in the electronic data capture system.

The procedures for these participants is limited to review of medical and research records and therefore the risks are minimal and limited to breach of confidentiality, their inclusion would not affect subjects' rights or welfare, and providing follow up information after participation is not applicable; as aforementioned, all eligible subjects and their data must be included in order to ensure generalizability of the results and the integrity of the data; data and PHI must be included in an identifiable format in order to link the data across timepoints and between the research/medical records and because there is overlap between the investigative teams between the two studies.

The waiver is requested in accordance with 45 CFR 46.116(d):

1) The research (continued use of the existing data) 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) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4) The research could not practicably be carried out without the waiver or alteration, and
5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

9.7.2 Waiver of Assent

The capability of all of the children is so limited that they cannot reasonably be consulted and the intervention involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and may be available only in the context of the research. A waiver of assent is approved by the CHOP IRB under 45 CFR 46.408(a) / 21 CFR 50.55(c)(1).

9.8 Compliance

9.8.1 Regulatory Compliance

This clinical trial will be conducted in accordance with the protocol, the ICH Harmonized Tripartite Guideline “Note for Guidance on Good Clinical Practice,” and the applicable local regulatory requirements. This study will be conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, the International Conference on Harmonization GCP Guideline applicable laws and regulations.

9.8.2 Investigator Assurances

Audits shall ensure that the study is planned, conducted, evaluated, and reported according this protocol and the applicable SOPs of the Coordinating Center, the ethical principles that have their origin in the Declaration of Helsinki (1996), the requirements of the ICH Harmonized Tripartite Guidelines.
Audits shall also ensure that the documentation of the study is available, complete, organized, and valid.
The investigator agrees to give the study monitor access to all relevant documents, including source documents, for review. The same applies in case of an inspection of federal authorities or the relevant IRB.

9.8.3 Records Retention and Requirements

The sponsor must archive all essential records and documents including but not limited to medical records, informed consent, and identification codes for subjects and other original records. These documents of the study will be retained in accordance with FDA record retention requirements, and will comply with CHOP policy A-3-9 for data retention.

9.8.4 Financial Disclosure

Financial disclosure information will be collected per Part 54 of Title 21 of the CFR and ICH E6. In addition, the site investigators must provide to the Study PI a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

9.8.5 Regulatory Files

Prior to beginning the study, the principal investigator and site investigators will be asked to comply with ICH E6 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- An original investigator-signed Investigator Agreement page of the protocol
- An IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardians
- IRB approval of the protocol and amendments
- Form FDA 1572, fully executed, and all updates on a new fully executed form FDA 1572, Curriculum vitae (CV) for the principal investigator and each sub investigator listed on Form FDA 1572. Current licensure must be noted on the CV. They will be signed and dated by the principal investigators and sub investigators at study start up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR and ICH E6. In addition, the Investigators must provide to the study PI a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.
- Laboratory certifications and normal ranges for any test or assay being performed.

9.8.6 Monitoring

The study will be monitored by the sponsor and co-investigators. Prior to trial initiation, trial readiness will be confirmed by the Office of Research Compliance (ORC) of CHOP, as assessed by the Pre-Trial Monitoring Visit. Periodic institutional monitoring will also be conducted according to ORC guidelines.
The investigator will ensure that the study team monitors according to the relevant standard operating procedures (SOPs) and GCP guidelines on a periodic basis to verify that data entries into the CRF are correct and that the study is conducted in accordance with this protocol.

9.8.7 Modification of the Protocol

Protocol modifications that affect the safety of the subjects or that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject selection criteria may be proposed by the principal investigator and the Medical Monitor. Any change to the protocol can be made only in the form of a written amendment to this study protocol. Such amendments must be approved by the CHOP IRB, and the FDA notified.

9.8.8 Protocol Violations

Protocol violations or deviations are any non-adherences to the procedures outlined in this document and include, but are not limited to, late evidence of exclusion criteria,

missed evaluations, incorrect timing of evaluations or dosing, and intake of inadmissible medication. After a subject has been enrolled, it is the investigator's responsibility to make any reasonable effort to avoid and, if necessary, correct protocol deviations. Major protocol violations will be reported to the DSMB at the time of a meeting, the IRB and the FDA. All protocol violations will be listed and the admissibility of the subjects' data will be discussed with the Medical Monitor prior to the statistical analysis. In case any emergency or AE occurs that requires a protocol deviation in the particular case, the investigator should contact the Medical Monitor and DSMB as soon as possible to enable a decision on whether the subject's participation in the study may be continued.

9.9 Payment to Subjects/Families

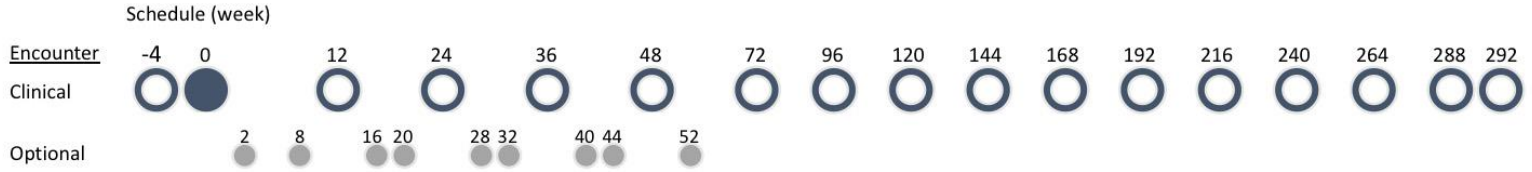
There will be no payment or re-imbursement to families or subjects.

10 PUBLICATION

Data sets will be made available to the scientific community after publication(s) of planned analyses (as set forth in the protocol) of the clinical trial results or no later than 3 years after the final visit of the last participant to a clinical trial site, whichever comes first. Data obtained in this trial will be presented in national and international meetings and will be published in the medical literature with no delays. The investigators are not under any agreement with the provider of the drug to limit or delay the publication of data from this trial.

APPENDIX

Appendix 1. Study Schedule, Overall



	Schedule (Week)																																						
	-4	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	60	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240	252	264	276	288	292
Clinical encounter	x	x				x			x			x			x			x		x		x		x		x		x		x		x		x		x	x
Optional encounter			x		x		x	x		x	x		x	x		x																						
Designation	V1	V2	V3	V4	V5	V201	V202	V203	V204	V205	V206	V207	V208	V209	V210	V211	V212	V213	V214	V215	V216	V217	V218	V219	V220	V221	V222	V223	V224	V225	V226	V227	V228	V229	V230	V231	V801

Appendix 2. Study Timeline*

Procedures performed solely for research purposes are indicated in bold text

		Screening	Baseline - Initial dosing	Treatment						Early Termination	Safety Closeout
Visit number	Required	1	2		4[p]		201[p]	204[o], 207[p], 210[o]	212[p], 213[o], 214[p], 215[o], 216[p], 217[o], 218[p], 219[o], 220[p], 221[o], 222[p], 223[o], 224[p], 225[o], 226[p], 227[o], 228[p], 229[o], 230[p],231[o]	ET[ap]	801[q]
	Optional[q]			3		5		202, 203, 205, 206, 208, 209, 211	212A, 213A, 214A, 215A, 216A, 217A, 218A, 219A, 220A, 221A, 222A, 223A, 224A, 225A, 226A, 227A, 228A, 229A, 230A		
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]	1-5	1-5	1-5	1-5	1-5	1-5	1-5	1-5
Visit window (days)[e]	—	2	±2	±2	±2	±2	±2	±5	±5	±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
Confirm tuberculosis test	—	X[f]									
Chest x-ray	—	X[g]									
Electrocardiogram (ECG)	—	X[r]									
Echo cardiogram	—	X[r]									
Review inclusion/	—	X									

exclusion criteria											
Medical history	—	X									
Physical examination	—	X	X	X	X	X	X	X	X	X	X
Vital signs	—	X	X	X	X	X	X	X	X	X	X
Diary Scores	—	X[i]	X	X	X	X	X	X	X	X	
Concomitant medications	—	X	X	X	X	X	X	X	X	X	X
Previous Therapy	—	X									
AGS scale, GMFM-88 and functional neurologic testing, CLASI	—	X						X[s]	X[s]		
Adverse events	—		X	X	X	X	X	X	X	X	X
Dispense baricitinib[k]	—		X					X	X		
Laboratory											
Hematology	—	X[h]	X[j]	X	X	X	X	X	X	X[w]	X[w]
Serum chemistry[v]	—	X[h]	X[j]	X	X	X	X	X	X	X[w]	X[w]
Lipid panel	—	X[h]				X	X	X	X	X[w]	
Urinalysis	—	X[h]	X[j]	X	X	X	X	X	X	X[w]	X[w]
IGF-1[x]	—		X					X	X		
Vitamin D							X[w]	X[w]	X[w]	X[w]	X[w]
HBsAg, HBcAb, HBsAb	—	X[l]									
Hepatitis C antibody	—	X[l]									

HIV		X[l]									
HSV, EBV, CMV	—	X[l]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]
Lymphocyte testing (T cell subset)	—	X[h]					X	X	X		
IgG	—	X[h]					X	X	X		
Cystatin C							X[w]	X[w]	X[w]	X[w]	X[w]
Thyroid stimulating hormone and T4	—	X[f]					X[w]	X[w]	X[w]	X[w]	X[w]
Serum pregnancy test[m]	—	X[h]									
Urine pregnancy test[m]	—		X	X	X	X	X	X	X		
BK virus serum[u]	—	X[h]	X	X		X	X	X	X	X[w]	X[w]
Serum baricitinib concentration[n]	—		X	X	X	X	X	X	X	X[w]	
IFN signaling score	—	X[t]	X	X	X	X	X	X	X	X[w]	X[w]
Hand/wrist/fingers X-rays[x]			X					X	X		

Abbreviations: ET = early termination; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; 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. Chest X ray will be performed on a clinical basis and results reviewed during screening. If chest x-ray was not performed clinically within 6 months prior to the study, it will be performed as part of the research study.
h. If results are available from testing within 1 month or as part of the pre-screening period, then the patient will not have to be retested at Visit 1.
i. At least 2 weeks of diary scores are required prior to beginning investigational product.

j. 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.
k. Drug will be dispensed at visit 2, visit 204, and then every 6 months during onsite visits. However, when traveling to the investigative site is not considered safe for the patients due to unforeseeable events (see footnote o), such as public or personal health emergencies, the study drug may be dispensed for a longer time.
l. If results are available from testing within the previous 3 months, then the patient will not have to be retested.
m. For female patients of child-bearing potential: a serum pregnancy test will be performed at Visit 1 and a urine pregnancy test (local laboratory) will be performed at Visit 2 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed.
n. Baricitinib concentration samples will be collected at on-site visits. Samples will be collected after beginning baricitinib therapy and at each dose escalation, and may be collected at each study visit for safety monitoring. However, when traveling to the investigative site is not considered safe for the patients due to unforeseeable events (see footnote o), such as public or personal health emergencies, baricitinib concentration samples will not be collected.
o. These required visits should be performed at the investigative site. However, in some circumstances, unforeseeable events, such as public health emergencies, states of emergency related to civil unrest, or weather emergencies, or individual health emergencies (affecting the patient or a caregiver), may create situations where it is unsafe for patients and their families to travel to the study site for in person assessments. In that case, the visits will be conducted using video operations. The changes from an in person evaluation, including differences to the study outcome collection, will be reported as a minor protocol deviation to the IRB at the time of continuing review.
p. 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. In addition, physical examination is not needed if a telephone visit is performed.
q. 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. Optional visits between weeks 60 to 288 would only be performed to allow patients to re-align with the initial in-person versus phone visits schedule, in cases where this schedule would be disrupted by an unforeseeable event (refer to footnote “o” for examples of such events) to enhance patients safety. For instance, if a patient were not able to come on-site for several months or years, an in-person visit may be necessary for the providers to assess the patient in-person.
r. EKG and echocardiogram will be performed on a clinical basis and reviewed during screening.
s. Functional outcome assessments will be conducted at baseline and every six months.
t. Three baseline IFN scores will be collected, each at least 5 days apart and not more than 60 days before start of study medication.
u. Patients will be monitored for BK viremia at baseline, and every six months until they reach two years of age. Over two years of age, complete follow-up BK testing will be performed if any of the following is observed: blood in urine (as defined by 5-10 RBCS in HPF), protein in urine (positive), decrease in eGFR (30 - <60 mL/min/1.73 m^2). Follow- BK testing includes urine and serum BK testing. Abnormal urine results with urinary tract infection, in the absence of change in eGFR, do not necessitate BK testing.
v. The creatinine should be measured using the IDMS (Isotopic Dilution Mass Spectrometry) technique to monitor the eGFR if available. Other methods are allowed but are not preferred. Laboratory testing using other methods will not be used to monitor the eGFR.
w. These labs may be drawn (optional).
x. For bone growth monitoring, IGF-1 will be completed yearly, and hand/wrist/fingers X-rays will be completed at baseline, 6 months, 12 months and then every 12 months (not after a bone age demonstrating complete growth).

* Visit schedule will be extended beyond Week 288 to long term follow up if transition to commercial supply is not possible for a patient. Visit will then be extended until patient transitions to commercial supply. The same tests and procedures that were completed during the study will be continued. Visit numbers will continue per the same numbering logic (232, 233, 234…).

Appendix 3. Dose Escalation Schedule for Patients with eGFR ≥60 mL/min/1.73 m2 or Normal eGFR for Age <24 Months (see footnote below[c])

If a change in the patient's weight during the study would place the patient in a different weight range, changes over time are permitted.

		Morning Dose	Noon Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Dosing Frequency
eGFR ≥ **60 mL/min/1.73 m^2**							
5-< 10 kg	Initial	1 mg	1 mg	0 mg	1 mg	3 mg	TID
	Escalation 1	1 mg	1 mg	1 mg	1 mg	4 mg	QID
10-< 20 kg	Initial	2 mg	2 mg	0 mg	2 mg	6 mg	TID
	Escalation 1	2 mg	2 mg	2 mg	2 mg	8 mg	QID
20-< 40 kg	Initial	3 mg	—	0 mg	3 mg	6 mg	BID
	Escalation 1	3 mg	—	2 mg	3 mg	8 mg	TID
≥ 40 kg	Initial	4 mg	—	—	4 mg	8 mg	BID
	Escalation 1	5 mg	—	—	5 mg	10 mg	BID
	Escalation 2	6 mg	—	—	6 mg	12 mg	BID

BID = twice daily, eGFR = estimated glomerular filtration rate, QID = 4 times daily, TID = 3 times daily.
a If there was a change in the patient's weight during the study, this would place the patient in a different weight range.
b Based on adult patient data as there is little data available in pediatric patients.
c. For the purposes of this protocol, we will define age based parameters for eGFR as follows: Normal renal function not requiring dose adjustments if: >12 months: At least a GFR of >60 ml/min/1.73 m2. <12 months: A GFR of >40 ml/min/1.73 m2. Patients will be excluded from enrollment if baseline eGFR was <30 ml/min/1.73 m2

The creatinine should be measured using the IDMS (Isotopic Dilution Mass Spectrometry) technique to monitor the eGFR if available. Other methods are allowed but are not preferred. Laboratory testing using other methods will not be used to monitor the eGFR.

The population PK analysis was updated including data from 71 juvenile and adolescent patients with Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE), CANDLE related disorders, STING-associated vasculopathy with onset in infancy (SAVI), and Aicardi-Goutières syndrome (AGS). The analysis has shown that while kidney function, as expressed by estimated GFR, is a statistically significant patient cofactor of the PK characteristics of baricitinib in this multi-disease patient population, the effects of eGFR on the kinetics of this patient population were not clinically relevant as they relate to dosing and did not support dose adjustment for patients with eGFR less than 120 mL/min/1.73 m^2.

Appendix 4. Dose Escalation Schedule for Patients with eGFR 30- <60 mL/min/1.73 m2 or for Age <24 Months with abnormal eGFR (see footnote below[c])

If a change in the patient's weight during the study would place the patient in a different weight range changes over time are permitted.

		Morning Dose	Noon Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Dosing Frequency
eGFR 30 - < **60 mL/min/1.73 m^{2}**[b]							
10-< 20 kg	Initial	1 mg	1 mg	0 mg	1 mg	3 mg	TID
	Escalation 1	1 mg	1 mg	1 mg	1 mg	4 mg	QID
20-< 40 kg	Initial	2 mg	—	—	1 mg	3 mg	BID
	Escalation 1	2 mg	—	—	2 mg	4 mg	BID
≥ 40 kg	Initial	2 mg	—	—	2 mg	4 mg	BID
	Escalation 1	3 mg	—	—	3 mg	6 mg	BID

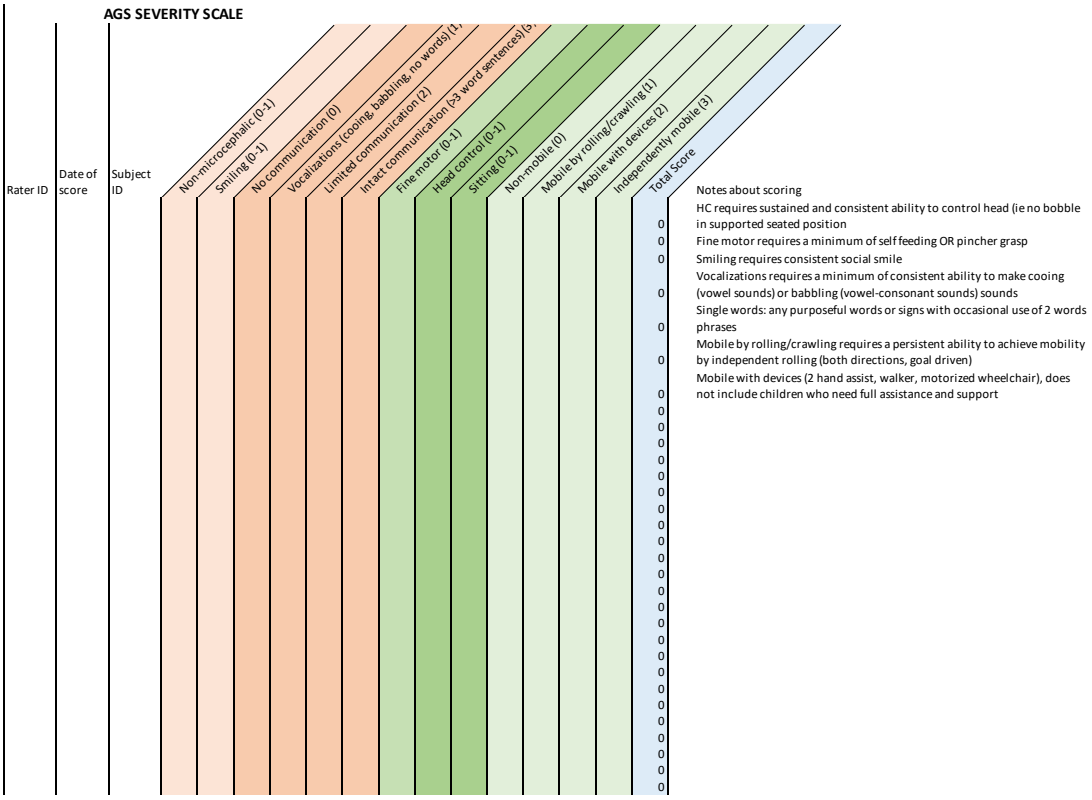
BID = twice daily, eGFR = estimated glomerular filtration rate, QID = 4 times daily, TID = 3 times daily.
a If there was a change in the patient's weight during the study, this would place the patient in a different weight range.
b Based on adult patient data as there is little data available in pediatric patients.
c. For the purposes of this protocol, we will define age based parameters for eGFR as follows: Normal renal function not requiring dose adjustments if: >12 months: At least a GFR of >60 ml/min/1.73 m2. <12 months: A GFR of >40 ml/min/1.73 m2. Patients will be excluded from enrollment if baseline eGFR was <30 ml/min/1.73 m2

The creatinine should be measured using the IDMS (Isotopic Dilution Mass Spectrometry) technique to monitor the eGFR if available. Other methods are allowed but are not preferred. Laboratory testing using other methods will not be used to monitor the eGFR.

The population PK analysis was updated including data from 71 juvenile and adolescent patients with Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE), CANDLE related disorders, STING-associated vasculopathy with onset in infancy (SAVI), and Aicardi-Goutières syndrome (AGS). The analysis has shown that while kidney function, as expressed by estimated GFR, is a statistically significant patient cofactor of the PK characteristics of baricitinib in this multi-disease patient population, the effects of eGFR on the kinetics of this patient population were not clinically relevant as they relate to dosing and did not support dose adjustment for patients with eGFR less than 120 mL/min/1.73 m^{2}.

JAK inhibitor treatment in Aicardi Goutières Syndrome

Appendix 5: AGS severity scale



Appendix 6. Patient Daily Diary for AGS infants 0-6 months

Age		0-6 months		
If G tube: poor feeding and regurgitation score maximum				
Medications:		Time medication was administered:		
System	Lilly categories	Signs and Symptoms	Yes/No	Score
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	❍
		Able to participate in the following with some level of disability: ambulation, communication or fine motor tasks at an age appropriate level		❍
		Requires functional or equipment support for any of the following: ambulation, communication or fine motor tasks at an age appropriate level		❍
		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		❍
	Crying	Cries but easily consolable	choose one of these	❍
		Excessive or high-pitched cry inconsolable for >2 minutes OR intermittently for <10 min		❍
		Excessive or high-pitched cry inconsolable for >2 minutes AND intermittently for <10 min		❍
		Excessive or high-pitched not consolable (cries >10 mins)		❍
	Length of uninterrupted sleep	Sleeps >3 hours continuously during night	choose one of these	❍
		Sleeps 2-3 hours continuously during night		❍
		Sleeps ≥ or =1 but <2 hours continuously during night		❍
		Sleeps <1 hours continuously during night		❍
	Excessive irritability	no irritability	choose one of these	❍
		consoling calms individual in <6 minutes		❍
		consoling calms individual in 6-15 minutes		❍
		consoling calms individual in >15 minutes or not at all		❍
		No startle reflex	choose one of these	❍
		Mild startle to noise		❍
		Strong startle reflex with noise		❍
		Strong startle reflex with noise including face grimacing, blinking and repeated jerks of arms		❍
		Any startle without noise		❍
		No tremors (shaking, jittering, or shivering movements of the extremities that are not seizures)	choose one of these	❍
		Tremors when disturbed (awoken from sleep, moved, or stimulated)		❍
		Tremors when undisturbed		❍
		No tone issues	choose one of these	❍
		Increased or decreased muscle tone (excessive stiffness or floppiness)		❍
	Generalized seizure	No convulsions or seizures	choose one of these	❍
		Experienced convulsions or seizures		❍
Other	Fever	No fever (temperature less than 98.9 F)	choose one of these	❍
		Low grade fever: 99 - 101 F (37.2-38.3 C)		❍
		Fever > 101.1 F (>38.4 C)		❍
		No feeding issues	choose one of these	❍
		Poor feeding (infrequent/uncoordinated suck or dependent on g-tube feeding)		❍
		No regurgitation/vomiting	choose one of these	❍
		Regurgitation/vomiting		❍
	Skin findings body	Skin findings: no skin problem	choose one of these	❍
		Skin findings: red patches which fade when pressed with fingers		❍
		Skin findings: red patches not fading when pressed with fingers		❍
		Skin findings: chronic discoloration		❍
	Skin findings hands, face, ears	Skin findings: no skin problem	choose one of these	❍
		Skin findings: red patches which fade when pressed with fingers		❍
		Skin findings: red patches not fading when pressed with fingers		❍
		Skin findings: chronic discoloration		❍
		Skin findings: no skin problem in any location	choose one of these	❍
		Skin findings: red patches which fade when pressed with fingers in any location		❍
		Skin findings: red patches not fading when pressed with fingers in any location		❍
		Skin findings: chronic discoloration in any location		❍

Appendix 7. Patient Daily Diary for AGS > 6 months

Age		6+ months		
If G tube: poor feeding and regurgitation score maximum				
Medications:		Time medication was administered:		
System	Lilly categories	Signs and Symptoms	Yes/No	Score
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	❍
		Able to participate in the following with some level of disability: ambulation, communication or fine motor tasks at an age appropriate level		❍
		Requires functional or equipment support for any of the following: ambulation, communication or fine motor tasks at an age appropriate level		❍
		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		❍
	Crying	Cries but easily consolable	choose one of these	❍
		Excessive or high-pitched cry inconsolable for >2 minutes OR intermittently for <10 min		❍
		Excessive or high-pitched cry inconsolable for >2 minutes AND intermittently for <10 min		❍
		Excessive or high-pitched not consolable (cries >10 mins)		❍
	Length of uninterrupted sleep	Sleeps >6 hours continuously during night	choose one of these	❍
		Sleeps 4-5 hour continuously during night		❍
		Sleeps 2-3 hours continuously during night		❍
		Sleeps <2 hours continuously during night		❍
	Excessive irritability	no irritability	choose one of these	❍
		consoling calms individual in <6 minutes		❍
		consoling calms individual in 6-15 minutes		❍
		consoling calms individual in >15 minutes or not at all		❍
		No startle reflex	choose one of these	❍
		Mild startle to noise		❍
		Strong startle reflex with noise		❍
		Strong startle reflex with noise including face grimacing, blinking and repeated jerks of arms		❍
		Any startle without noise		❍
		No tremors (shaking, jittering, or shivering movements of the extremities that are not seizures)	choose one of these	❍
		Tremors when disturbed (awoken from sleep, moved, or stimulated)		❍
		Tremors when undisturbed		❍
		No tone issues	choose one of these	❍
		Increased or decreased muscle tone (excessive stiffness or floppiness)		❍
	Generalized seizure	No convulsions or seizures	choose one of these	❍
		Experienced convulsions or seizures		❍
Other	Fever	No fever (temperature less than 98.9 F)	choose one of these	❍
		Low grade fever: 99 - 101 F (37.2-38.3 C)		❍
		Fever > 101.1 F (>38.4 C)		❍
		No feeding issues	choose one of these	❍
		Poor feeding (infrequent/uncoordinated suck or dependent on g-tube feeding)		❍
		No regurgitation/vomiting	choose one of these	❍
		Regurgitation/vomiting		❍
	Skin findings body	Skin findings: no skin problem	choose one of these	❍
		Skin findings: red patches which fade when pressed with fingers		❍
		Skin findings: red patches not fading when pressed with fingers		❍
		Skin findings: chronic discoloration		❍
	Skin findings hands, face, ears	Skin findings: no skin problem	choose one of these	❍
		Skin findings: red patches which fade when pressed with fingers		❍
		Skin findings: red patches not fading when pressed with fingers		❍
		Skin findings: chronic discoloration		❍
		Skin findings: no skin problem in any location	choose one of these	❍
		Skin findings: red patches which fade when pressed with fingers in any location		❍
		Skin findings: red patches not fading when pressed with fingers in any location		❍
		Skin findings: chronic discoloration in any location		❍

Appendix 8. Clinical Laboratory Tests

Hematology[a,b,c]

Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume (MCV)
Mean cell hemoglobin concentration (MCHC)
Leukocytes (WBC)
Reticulocyte
Absolute counts of:
Neutrophils, segmented
Neutrophils, juvenile (bands)
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets
Cell Morphology
Lymphocyte subset testing
IgG

Lipid[e]

Total cholesterol (TC)
Low-density lipoprotein (LDL)
High-density lipoprotein (HDL)
Triglycerides

Urinalysis[a,b,f]

Color
Specific gravity
pH
Protein
Glucose
Ketones
Bilirubin
Urobilinogen
Blood
Leukocyte esterase
Nitrite

Serum Chemistry[a,b]

Sodium
Potassium
Total bilirubin[c]
Direct bilirubin[c]
Alkaline phosphatase
Alanine aminotransferase (ALT/SGPT)[c]
Aspartate aminotransferase (AST/SGOT)[c]
Blood urea nitrogen (BUN)[c]
Creatinine[c]
Calcium
Glucose
Albumin
Total protein
Creatine phosphokinase (CPK)
Uric acid
Gamma glutamyl transferase (GGT)
Aldolase[d]
INR[k]
PT[k]

Other Tests[a]

Hepatitis B Surface antigen (HBsAg)[g]
Anti-Hepatitis B Core antibody (HBcAb)[g]
Hepatitis B Surface antibody (HBsAb)[g]
Hepatitis B Virus DNA[g]
Human immunodeficiency virus (HIV)[g]
Hepatitis C antibody[h]
Thyroid-stimulating hormone (TSH)
Thyroxine (T4)
Pregnancy Testing
QuantiFERON®-TB Gold[g,j]
Baricitinib serum concentration
BK virus PCR in plasma
BK virus PCR in urine
EBV PCR in plasma-quantitative
CMV PCR in plasma-quantitative
HSV IgG and IgM
IGF-1
Vitamin D
Cystatin C

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.

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
d. Perform if inflammatory myositis is present.
e. Lipid profile.
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, unless the DSMB rules that the finding is likely related to underlying autoimmunity in AGS and not to TB infection.
k. At baseline only.

Appendix 9. Management of Liver Enzyme Laboratory values

Clinical laboratory investigation is needed for diagnosis and monitoring based of liver involvement in AGS. One-third of individuals with AGS have baseline hepatic involvement (AST/ALT >3 x ULN and GGT>2.5 ULN). Therefore using the Drug Induced Liver Injury Guidance published by the FDA in July 2009 is not applicable. Thus, the following liver enzyme laboratory testing monitoring is proposed:

- Laboratory screening of hepatic function panel and or comprehensive metabolic panel (including AST, ALT, total and direct or conjugated bilirubin, ALK, GGT and albumin) will be tested according to study schedule.
- At baseline, Model for End-Stage Liver Disease (MELD) (in individuals >12 years) and the Pediatric End-Stage Liver Disease (PELD) tools will be used to assess for underlying hepatic dysfunction. Individuals with scores of >15 will prohibit enrollment.
- If an isolated elevation of ALT/AST>1000 U/L is seen, or direct bilirubin elevation >3x ULN, this will result in updated calculation of the MELD or PELD as age appropriate, and individuals with scores of >15 will be considered for drug tapering and cessation as well as referral to a hepatologist.
- If during study, or prior to enrollment, AST/ALT elevations of >5x ULN are seen, this will result in repeating liver enzyme and serum bilirubin tests weekly. Frequency of retesting can decrease to once a month or less if abnormalities stabilize or the investigational product has been discontinued and the patient is asymptomatic.

In addition, the following assessments will be performed:

- 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 where clinically indicated; repeating EBV and CMV PCR; autoimmune markers; nonalcoholic steatohepatitis; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents (for example, occupational or recreational exposure)
- Consider obtaining gastroenterology or hepatology consultations

PELD_score = 10 * ((0.480 * ln(Bilirubin)) + (1.857 * ln(INR)) - (0.687 * ln(Albumin)) + Listing_age_factor + Growth)

Input:

Sex	○ Female ○ Male	
Age		yr ▾
Weight		kg ▾
Height		cm ▾
Albumin		g/dL ▾
Bilirubin		mg/dL ▾
INR		
Listing	○ Age at listing one year or older ○ Age at listing less than one year	
Exception diagnoses	○ Noncontributory ○ Urea cycle disorder ○ Organic acidemia ○ Hepatoblastoma	

Results:

Growth failure	
PELD score	

Reset form

MELD_score = (Round the following expression to the nearest integer)((9.57 * ln(Creatinine/88.4)) + (3.78 * ln(Bilirubin/17.1)) + (11.2 * ln(INR)) + 6.43)
MELDNa_score = MELD_score + ((1 if the following expression is true, 0 if false)(MELD_score > 11)) * ((1.32 * (137 - Serum_Na)) - (0.033 * MELD_score * (137 - Serum_Na)))

Input:

Creatinine		mcmol/L ▾
Serum Na		mmol/L ▾
Bilirubin		mcmol/L ▾
INR		
Hemodialysis twice or ≥24 hours of CVVHD in the past week	○ Yes ◉ No	

Results:

MELD score	
MELDNa score	

Reset form

Appendix 10. Management of Leukocyte associated laboratory testing and IgG

Exclusion criteria specific to leukocytes:

- Neutropenia (absolute neutrophil count [ANC] <500 cells/μL)
- CD4 <250 cell/μl on lymphocyte subset testing (where Absolute CD4 count=Absolute CD3/CD4 count=CD3/CD4 count=CD4 count=Absolute CD3+CD4+ cells)
- Patients not meeting criteria can follow protocols for further diagnosis and management and be reconsidered for enrollment at a later time

Criteria for consideration of drug tapering and discontinuation:

- IF ANC 750<1000, THEN follow CBC Q 2 weeks until ANC≥1000
- IF ANC 500<750, THEN follow CBC weekly until ANC≥1000.
- IF ANC 250<500, repeat within 48h and if persistent, refer to local immunology or infectious disease clinical team to start ID ppx (as per flowchart below) and consider G-CSF. Repeat weekly thereafter until ANC ≥1000.
- IF ANC <250, repeat within 48h and if persistent, refer to local immunology or infectious disease clinical team to start ID ppx (as per flowchart below) and consider G-CSF. Repeat weekly thereafter until ANC ≥1000.
- If <250 persists > 7 days, refer to local immunology or infectious disease clinical team to start G-CSF and continue to repeat weekly.
    - If <250 persists >14 days after starting G-CSF, decrease dose to next dose increment (ie if 2mg tid decrease to 2mg bid) (Appendix 14) and continue to repeat weekly.
    - If <250 persists >14 days after starting G-CSF and dose reduction, taper to stop baricitinib.

- IF ALC 250<500, THEN follow CBC Q 2 weeks until ALC≥500 AND start ID ppx (as per flowchart below).
- IF ALC <250, THEN follow CBC weekly until ALC ≥250 AND refer to local immunology or infectious disease clinical team to start ID ppx (as per flowchart below).
- IF ALC <250
    - If <250 persists > 7 days, repeat 1 week later.
    - If <250 persists >14 days, decrease dose to next dose increment (ie if 2mg tid decrease to 2mg bid) (Appendix 14) and continue to repeat 7 days and 14 days later.
    - If <250 persists >14 days after dose reduction, taper to stop baricitinib.

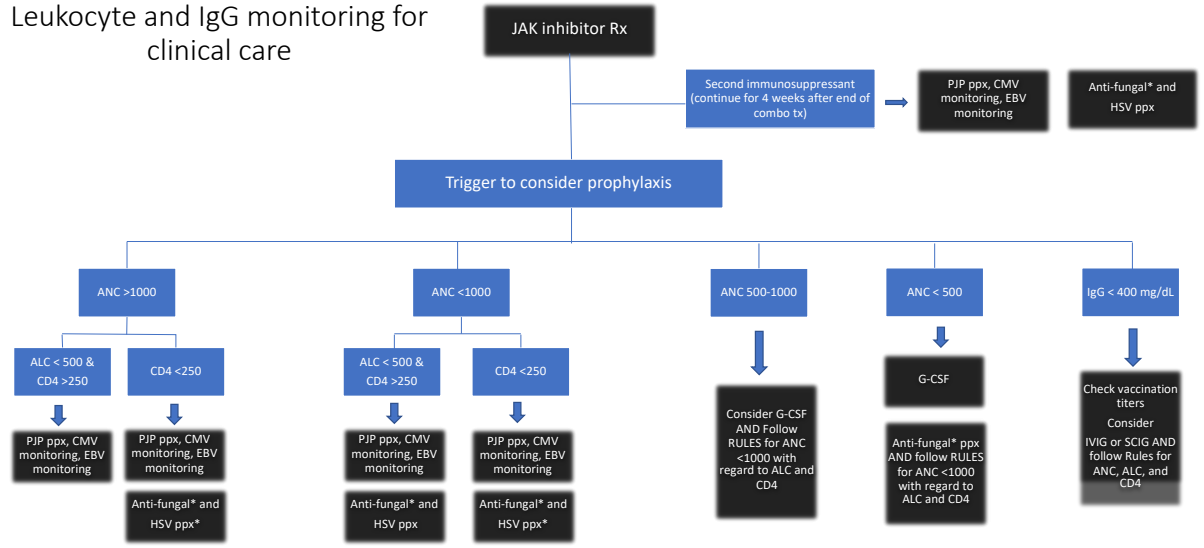
Management of immunologic abnormalities

- When these immunologic abnormalities occur, clinical management recommendations below will be shared with the local team in the form of a letter

via email or fax, to enable the clinical team caring for the patient to use these best practices.

- General recommendations for clinical management of immunologic abnormalities are detailed below, however deviations from this approach by the clinician caring for the patient, during the clinical care of this individual, will not be considered a protocol deviation. The investigative team will retain decision making about drug discontinuation based on the above recommendations.
- Specifically, the use of specific prophylactic agents, G-CSF and GM-CSF may be at the clinician's discretion, for example even if the criteria below for neutropenia are not met, based on the child's overall health and any contraindications (renal function or other medications for example).

For management of leukocyte laboratory abnormalities



Antifungal ppx should be with a drug that covers mold: posaconazole, voriconazole, itraconazole, or caspofungin
PJP ppx: First-line bactrim; Second-line: dapsone, atovaquone, or pentamidine
HSV ppx: acyclovir or valacyclovir
Second immunosuppressant = Prednisone equivalent >=0.3mg/kg/day or Prednisone equivalent >10mg daily OR tacrolimus, sirolimus, cyclosporine, cyclophosphamide, mercaptopurine, mycophenolate mofetil, methotrexate (>=30mg/m2/week), a cytokine blocker, or any chemotherapeutic

Appendix 11. Management of Anemia

Exclusion criteria specific to anemia:

- Hemoglobin <7 mg/dL (70 g/L) will not be enrolled
- Hemoglobin <8 mg/dl will be used as a threshold in infants <2 months
- Patients not meeting criteria can follow protocols for further diagnosis and management and be reconsidered for enrollment at a later time

Criteria for consideration of drug tapering and discontinuation:

- Patients who develop a hemoglobin (Hg) of <7gm/dl*, should be transfused PRBCS as per institutional practice and a post transfusion Hg be measured weekly.
- Patients who develop a hemoglobin (Hg) of <7gm/dl* within <4 weeks of the transfusion should taper baricitinib to next dose increment (e.g. 2 mg tid to 2 mg bid) and be transfused PRBCS as per institutional practice and a post transfusion Hg be measured weekly.
- Patients who develop a hemoglobin (Hg) of <7gm/dl* within <4 weeks of the transfusion should taper baricitinib to next dose increment (e.g. 2 mg bid to 1 mg bid) and be transfused PRBCS as per institutional practice and a post transfusion Hg be measured weekly.
- If hemoglobin (Hg) of <7gm/dl* after two dose reductions, baricitinib should be tapered to cessation.
- Patients who develop a hemoglobin <5gm/dl at any time should taper baricitinib to cessation and be removed from protocol therapy*.
- Patients may dose escalate in a stepwise fashion after Hg>8gm/dl for >4 weeks.

* if acute blood loss in the context of GI bleeding, surgery, documented immune mediated hemolysis or anemia or an accident is the cause of the acute anemia, treatment of the underlying cause prior to drug tapering is warranted prior to drug tapering. Hemoglobin <8 mg/dl will be used as a threshold in infants <2 months.
For patients who have been taking baricitinib for > 2 weeks and develop >50% drop in hemoglobin from baseline should have following work-up at minimum: CBC, reticulocyte count, LDH, haptoglobin, DAT, C5b-9, review of peripheral blood smear. Consider consultation with pediatric hematologist.

Management of anemia

- When these hematologic abnormalities occur, clinical management recommendations above will be shared with the local team in the form of a letter via email or fax, to enable the clinical team caring for the patient to use these best practices. The investigative team will retain decision making about drug discontinuation based on the above recommendations.
- General recommendations for clinical management of anemia are detailed above, however deviations from this approach by the clinician caring for the patient, during the clinical care of this individual, will not be considered a protocol

deviation. An example, would be the use of a transfusion at a level higher than the above protocol stipulates, felt to be best taking into consideration the overall health of the patient. Specifically, the use of EPO may be at the clinician's discretion. The investigative team will retain decision making about drug discontinuation based on the above recommendations.

Appendix 12. Management of Thrombocytopenia and Thrombocytosis

Exclusion criteria specific to thrombocytopenia/thrombocytosis:

- Thrombocytopenia (platelets <30,000/μL).
- Patients who are on anticoagulation or having a history of life-threatening bleeding should be excluded if platelet count is <50,000/μL.
- Patients not meeting criteria can follow protocols for further diagnosis and management and be reconsidered for enrollment at a later time.

Criteria for consideration of drug tapering and discontinuation for thrombocytopenia:

- Patients who develop a platelet count of <20,000/ μL ** should be transfused as per institutional practice. Platelets should be rechecked weekly. If bleeding symptoms occur, platelets should be rechecked sooner.
- Patients who develop a platelet count of <20,000/ μL ** within <4 weeks of transfusion should be transfused as per institutional practice and should taper baricitinib to next dose increment (e.g. 2 mg tid to 2 mg bid). Platelets should be rechecked weekly. If bleeding symptoms occur, platelets should be rechecked sooner.
- Patients who develop a platelet count of <20,000/ μL ** after dose reduction should be transfused as per institutional practice and should taper baricitinib to next dose increment (e.g. 2 mg bid to 1 mg bid). Platelets should be rechecked weekly. If bleeding symptoms occur, platelets should be rechecked sooner.
- Patients who develop a platelet count of <20,000/ μL ** after two dose reductions, baricitinib should be tapered to cessation.
- Patients who develop a platelet count <10,000/ μL at any time should taper baricitinib should be tapered to cessation and permanently discontinued.
- Patients may dose escalate in a stepwise fashion after 4 weeks of stability of platelets > 70,000/ μL.
- Patients with a history of non CNS bleeding should taper baricitinib to the next dose increment if platelet count falls below 30,000/ μL and be transfused. Patients with a history of bleeding or taking anticoagulation cannot be dose escalated. If platelet count drops <30,000/ μL at decreased dosing (Appendix 14), baricitinib should be tapered to cessation and permanently discontinued.
- Patients with a history of CNS bleeding or taking anticoagulation should taper baricitinib to the next dose increment (Appendix 14) if platelet count falls below 50,000/ μL and be transfused. Patients with a history of bleeding or taking anticoagulation cannot be dose escalated. If platelet count drops <50,000/ μL at decreased dosing (Appendix 14), baricitinib should be tapered to cessation and permanently discontinued.

  ** if documented immune mediated thrombocytopenia is the cause, treatment of the underlying cause prior to drug tapering is warranted prior to drug tapering. For patients who have been taking baricitinib for > 2 weeks and develop >50% drop in platelet count should have following work-up at

minimum: CBC, reticulocyte count, LDH, haptoglobin, DAT, C5b-9, review of peripheral blood smear. Consider consultation with pediatric hematologist.

Criteria for consideration of drug tapering and discontinuation for thrombocytosis:

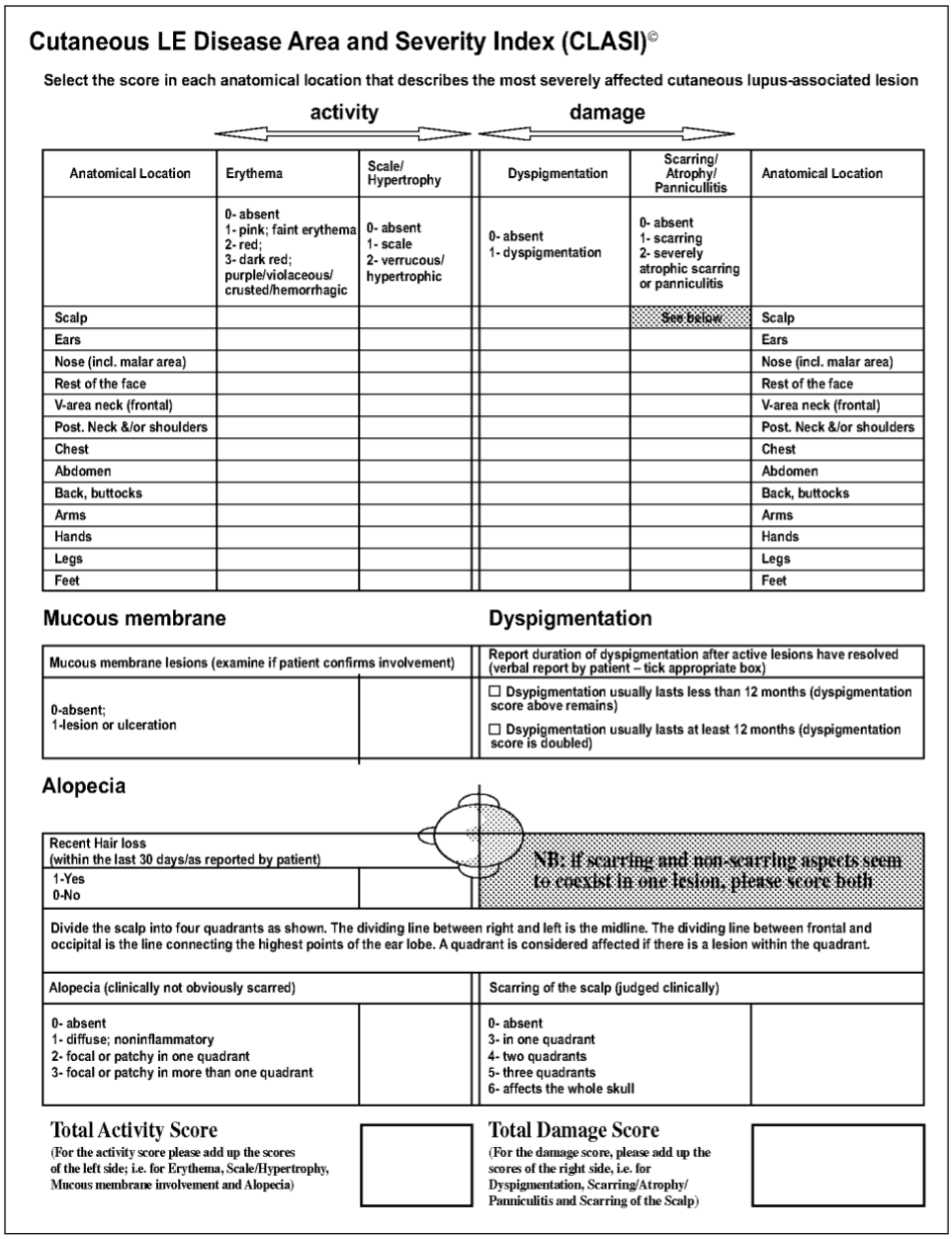
- Patients who do not have a known vasculopathy and who develop a platelet count of >1,000,000/ µL *** should be rechecked < 1 week.
- If platelets remain >1,000,000/ µL ***, they should taper baricitinib to next dose increment (e.g. 2 mg tid to 2 mg bid). Platelets should be rechecked weekly.
- If platelets remain >1,000,000/ µL *** after dose reduction, they should taper baricitinib to next dose increment (e.g. 2 mg bid to 1 mg bid). Platelets should be rechecked weekly.
- If persistent platelets > 1,000,000/ µL *** after >14 days, should taper baricitinib to discontinuation.
- Patients may dose escalate in a stepwise fashion after 4 weeks of stability of platelets <800,000/ µL.
- For individuals with known CNS vasculopathy (e.g. prior strokes, moya moya), take same measures for platelet counts ≥ 800,000/mcL.
- Consider consultation with pediatric hematologist.

***Consider if there is an alternative explanation (such as intercurrent illness as platelets are an acute phase reactant).

Management of Thrombocytopenia and Thrombocytosis

- When these abnormalities occur, clinical management recommendations above will be shared with the local team in the form of a letter via email or fax, to enable the clinical team caring for the patient to use these best practices
- General recommendations for clinical management of thrombocytopenia and thrombocytosis are detailed above, however deviations from this approach by the clinician caring for the patient, during the clinical care of this individual, will not be considered a protocol deviation. The investigative team will retain decision making about drug discontinuation based on the above recommendations.

Appendix 13. Cutaneous LE Disease Area and Severity Index (CLASI)



Cutaneous LE Disease Area and Severity Index (CLASI)©

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

activity ⟷ damage

Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0- absent 1- pink; faint erythema 2- red; 3- dark red; purple/violaceous/ crusted/hemorrhagic	0- absent 1- scale 2- verrucous/ hypertrophic	0- absent 1- dyspigmentation	0- absent 1- scarring 2- severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane **Dyspigmentation**

Mucous membrane lesions (examine if patient confirms involvement)		Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)
0-absent; 1-lesion or ulceration		☐ Dsypigmentation usually lasts less than 12 months (dyspigmentation score above remains) ☐ Dsypigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

Recent Hair loss (within the last 30 days/as reported by patient) 1-Yes 0-No		NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0- absent 1- diffuse; noninflammatory 2- focal or patchy in one quadrant 3- focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score
(For the activity score please add up the scores of the left side; i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score
(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/ Panniculitis and Scarring of the Scalp)

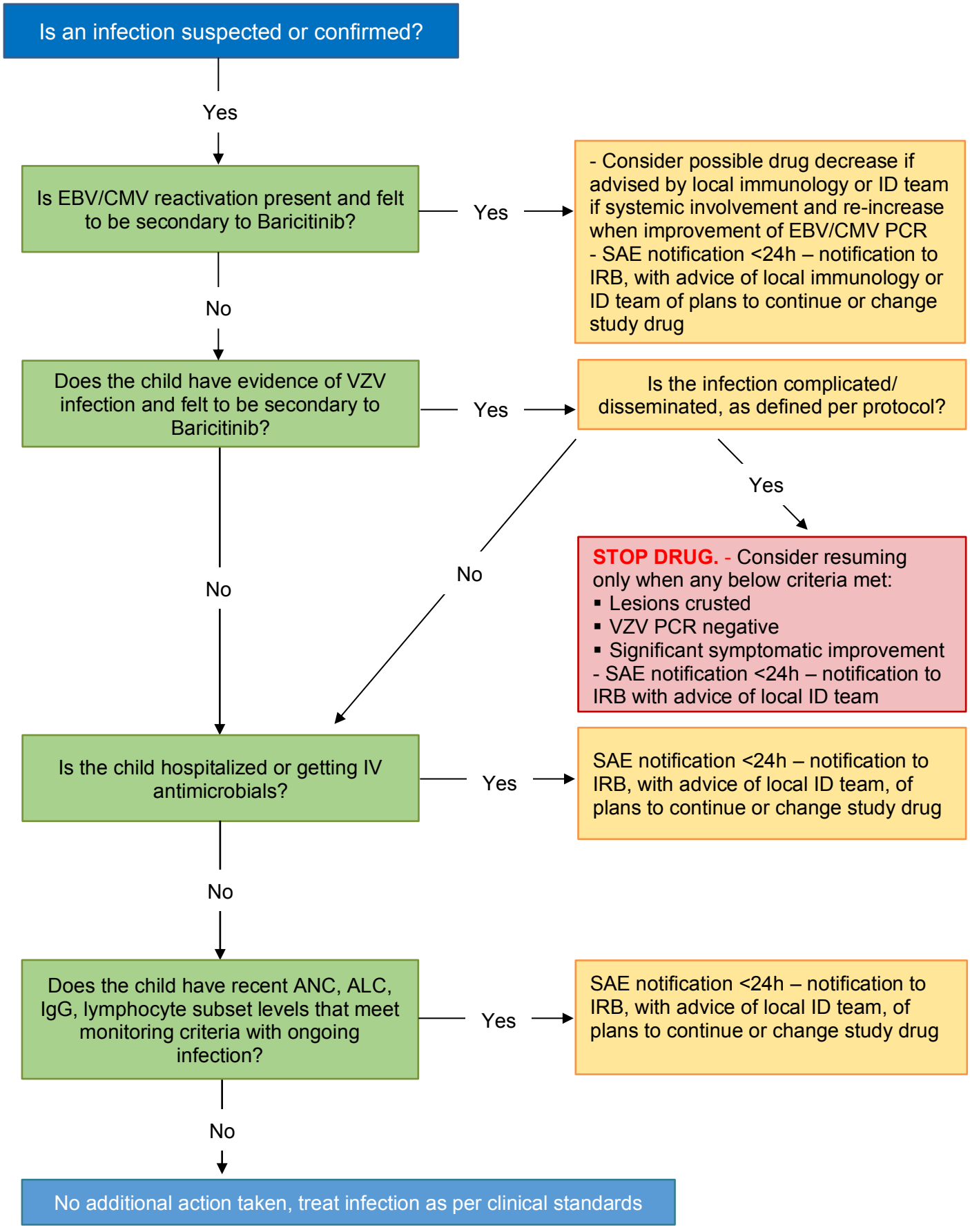
Figure 1. The Cutaneous Lupus Erythematosus Disease Area and Severity Index. Reprinted by permission from the University of Pennsylvania, copyright 2009.

Appendix 14. Dose tapering guidance

The following serves as guidance for dose tapering if necessary due to subject tolerance. If dose tapering is conducted for subject preference, dose tapering may occur more slowly, as needed for subject tolerance.
in two week increment unless resolution of AE requiring tapering
* smaller dose increments obtained by pill cutter, until small pill size can be provided to patient where available

Initial dose	Dose decrease 1 #	Dose decrease 2 #	Dose decrease 3 #	Dose decrease 4 #	Dose decrease 5 #
1 mg bid	1 mg am and 0.5 mg* pm	0.5 mg* bid	0.5 mg am	stop	
1 mg tid	1 mg bid	1 mg am and 0.5 mg* pm	0.5 mg* bid	0.5 mg am	stop
1 mg qid	1 mg tid	1 mg bid	1 mg am and 0.5 mg* pm	0.5 mg* bid	stop
2 mg bid	1 mg tid	1 mg bid	1 mg am and 0.5 mg* pm	0.5 mg* bid	stop
2 mg tid	2 mg bid	1 mg * tid	1 mg * bid	0.5 mg* bid	stop
2 mg qid	2 mg tid	2 mg bid	1 mg * tid	1 mg* bid	stop
3 mg bid	2 mg bid	1 mg * tid	1 mg * bid	0.5 mg* bid	stop
3-2-3 mg	2 mg tid	2 mg bid	1 mg * tid	1 mg * bid	stop
3 mg qid	3-2-3-2 mg	2 mg qid	2-1-2-1 mg	1 mg qid	stop
4 mg bid	2 mg tid	2 mg bid	1 mg * tid	1 mg* bid	stop
4-2-4 mg	2 mg* qid	2 mg tid	2 mg bid	1 mg bid	stop
5 mg bid	4 mg bid	2 mg tid	2 mg bid	1 mg bid	stop
4 mg tid	2 mg* qid	2 mg tid	2 mg bid	1 mg bid	stop
6 mg bid	5 mg bid	4 mg bid	2 mg tid	2 mg bid	stop

Appendix 15. Decision tree in case of infection suspicion or confirmation



Appendix 16. Concomitant medication approach in patients with AGS receiving baricitinib

The information below is based on a review of Lexicomp and the published prescribing information on April 4, 2020.

1. Permitted

Permitted medications include any other standard therapy used to manage signs and symptoms of AGS that does not interact to any significant extent with baricitinib (see sections 2 and 3). These may include, but are not limited to, medications used to manage tone, seizure medications, medications to manage reflux and constipation as examples.

2. Use with caution

This section includes medications that interact with baricitinib but are not absolutely contraindicated. If a medication may be used, a dosage adjustment of either the study drug or the concomitant medication may be warranted. CYP3A4 is identified as the main metabolizing enzyme and in vitro studies indicate that baricitinib does not significantly inhibit or induce the activity of cytochrome P450 enzymes (CYPs 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6) or inhibit transporters Pgp or OATP 1B1. Renal elimination is the principal clearance mechanism and baricitinib is identified as a substrate of OAT3, Pgp, BCRP and MATE2-K from *in vitro* studies.

In the following medications, patients should be monitored for safety parameters after initiation, but these are not absolutely contraindicated:

- Chloramphenicol (Ophthalmic)
- CloZAPine
- Coccidioides immitis Skin Test
- Promazine/chlorpromazine

Therapy modification may be necessary in the following medications, including due to OAT1/3 metabolism interference:

- Echinacea: May diminish the therapeutic effect of Immunosuppressants
- Probenecid
- Nitisinone
- Pretomanid
- Tolvaptan (brand specific- Jynarque®)

Of note regarding vaccinations:

- Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy,

revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

- Smallpox and Monkeypox Vaccine (Live) may be given if it is the brand vaccine Jynneos; this is a live, attenuated, non-replicating vaccine that is effective against both smallpox and monkeypox. This excludes the smallpox vaccine which is a live replicating vaccine. If this vaccine is given the following should be noted: Immunosuppressants may diminish the therapeutic effect of Smallpox and Monkeypox Vaccine (Live).

Although the following are not absolutely contraindicated in the context of baricitinib use, in the context of this trial, if they need to be initiated, baricitinib will be tapered to cessation when use is initiated:

- Azathioprine
- Cyclosporine is not recommended.
- Antirheumatic doses of methotrexate
- Nonbiologic disease modifying antirheumatic drugs (DMARDs)
- Deferiprone
- Denosumab
- Fingolimod
- Leflunomide
- Mesalamine
- Nivolumab
- Roflumilast
- Sipuleucel-T
- Pidotimod
- Tertomotide
- Trastuzumab

3. Prohibited

The following are medications that cannot be administered to a patient enrolled on the study under any circumstance:

- BCG (Intravesical).
- Belimumab
- Biologic Disease-Modifying Antirheumatic Drugs (DMARDs)
- Cladribine
- Dipyrone
- Natalizumab
- Pimecrolimus
- Tacrolimus (Topical)
- Vaccines (Live) **Exceptions:** Smallpox and Monkeypox Vaccine (Live) if it is the brand vaccine Jynneos.

References

1 Bonkowsky, J. L. *et al.* The burden of inherited leukodystrophies in children. *Neurology* **75**, 718-725 (2010). https://doi.org:10.1212/WNL.0b013e3181eee46b

2 Crow, Y. J. *et al.* Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. *Am J Med Genet A* **167A**, 296-312 (2015). https://doi.org:10.1002/ajmg.a.36887

3 Rice, G. *et al.* Clinical and molecular phenotype of Aicardi-Goutieres syndrome. *The American Journal of Human Genetics* **81**, 713-725 (2007).

4 Rice, G. I. *et al.* Assessment of interferon-related biomarkers in Aicardi-Goutieres syndrome associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, and ADAR: a case-control study. *The Lancet Neurology* **12**, 1159-1169 (2013).

5 Vanderver, A. *et al.* Early-Onset Aicardi-Goutieres Syndrome: Magnetic Resonance Imaging (MRI) Pattern Recognition. *J Child Neurol* **30**, 1343-1348 (2015). https://doi.org:10.1177/0883073814562252

6 Crow, Y. J. *et al.* Mutations in the gene encoding the 3′-5′ DNA exonuclease TREX1 cause Aicardi-Goutieres syndrome at the AGS1 locus. *Nature genetics* **38**, 917-920 (2006).

7 Rice, G. I. *et al.* Mutations involved in Aicardi-Goutieres syndrome implicate SAMHD1 as regulator of the innate immune response. *Nature genetics* **41**, 829-832 (2009).

8 Rice, G. I. *et al.* Gain-of-function mutations in IFIH1 cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling. *Nature genetics* **46**, 503-509 (2014).

9 Rice, G. I. *et al.* Mutations in ADAR1 cause Aicardi-Goutieres syndrome associated with a type I interferon signature. *Nature genetics* **44**, 1243-1248 (2012).

10 Lebon, P. *et al.* Intrathecal synthesis of interferon-alpha in infants with progressive familial encephalopathy. *J Neurol Sci* **84**, 201-208 (1988).

11 Goutieres, F., Aicardi, J., Barth, P. G. & Lebon, P. Aicardi-Goutieres syndrome: an update and results of interferon-alpha studies. *Ann Neurol* **44**, 900-907 (1998). https://doi.org:10.1002/ana.410440608

12 Akwa, Y. *et al.* Transgenic expression of IFN-alpha in the central nervous system of mice protects against lethal neurotropic viral infection but induces inflammation and neurodegeneration. *J Immunol* **161**, 5016-5026 (1998).

13 van Heteren, J. T. *et al.* Astrocytes produce interferon-alpha and CXCL10, but not IL-6 or CXCL8, in Aicardi-Goutieres syndrome. *Glia* **56**, 568-578 (2008). https://doi.org:10.1002/glia.20639

14 Klok, M. D. *et al.* Interferon-alpha and the calcifying microangiopathy in Aicardi-Goutieres syndrome. *Ann Clin Transl Neurol* **2**, 774-779 (2015). https://doi.org:10.1002/acn3.213

15 Barth, P. G. The neuropathology of Aicardi-Goutieres syndrome. *Eur J Paediatr Neurol* **6 Suppl A**, A27-31; discussion A37-29, A77-86 (2002).

16 Kavanagh, D. *et al.* Type I interferon causes thrombotic microangiopathy by a dose-dependent toxic effect on the microvasculature. *Blood* **128**, 2824-2833 (2016). https://doi.org:10.1182/blood-2016-05-715987

17 Adang, L., Goldbach-Mansky, R. & Vanderver, A. JAK Inhibition in the Aicardi-Goutières Syndrome. Reply. *N Engl J Med* **383**, 2191-2193 (2020). https://doi.org:10.1056/NEJMc2031081
18 Vanderver, A. *et al.* Janus Kinase Inhibition in the Aicardi-Goutieres Syndrome. *N Engl J Med* **383**, 986-989 (2020). https://doi.org:10.1056/NEJMc2001362
19 Piccoli, C. *et al.* Late-Onset Aicardi-Goutieres Syndrome: A Characterization of Presenting Clinical Features. *Pediatr Neurol* **115**, 1-6 (2021). https://doi.org:10.1016/j.pediatrneurol.2020.10.012
20 Uggenti, C. *et al.* cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing. *Nat Genet* **52**, 1364-1372 (2020). https://doi.org:10.1038/s41588-020-00737-3
21 Valentino, L. & Pierre, J. JAK/STAT signal transduction: regulators and implication in hematological malignancies. *Biochem Pharmacol* **71**, 713-721 (2006). https://doi.org:10.1016/j.bcp.2005.12.017
22 Kremer, J. M. *et al.* The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum* **60**, 1895-1905 (2009). https://doi.org:10.1002/art.24567
23 Boy, M. G. *et al.* Double-blind, placebo-controlled, dose-escalation study to evaluate the pharmacologic effect of CP-690,550 in patients with psoriasis. *J Invest Dermatol* **129**, 2299-2302 (2009). https://doi.org:10.1038/jid.2009.25
24 Takanohashi, A. *et al.* Elevation of proinflammatory cytokines in patients with Aicardi-Goutieres syndrome. *Neurology* **80**, 997-1002 (2013). https://doi.org:10.1212/WNL.0b013e3182872694
25 Sparrow SS, C. D., Balla DA. . *Vineland Adaptive Behavior Scales: Second edition.* . (American Guidance Service, 2005).
26 Kim, H. *et al.* Pharmacokinetics, Pharmacodynamics, and Proposed Dosing of the Oral JAK1 and JAK2 Inhibitor Baricitinib in Pediatric and Young Adult CANDLE and SAVI Patients. *Clin Pharmacol Ther* (2017). https://doi.org:10.1002/cpt.936
27 Adang, L. A. *et al.* Aicardi goutieres syndrome is associated with pulmonary hypertension. *Molecular genetics and metabolism* **125**, 351-358 (2018). https://doi.org:10.1016/j.ymgme.2018.09.004
28 Austin, E. D. & Loyd, J. E. The genetics of pulmonary arterial hypertension. *Circulation research* **115**, 189-202 (2014). https://doi.org:10.1161/circresaha.115.303404
29 George, P. M. *et al.* Evidence for the involvement of type I interferon in pulmonary arterial hypertension. *Circulation research* **114**, 677-688 (2014). https://doi.org:10.1161/circresaha.114.302221
30 Ma, L. & Chung, W. K. The role of genetics in pulmonary arterial hypertension. *The Journal of pathology* **241**, 273-280 (2017). https://doi.org:10.1002/path.4833
31 Huertas, A. *et al.* Immune dysregulation and endothelial dysfunction in pulmonary arterial hypertension: a complex interplay. *Circulation* **129**, 1332-1340 (2014). https://doi.org:10.1161/circulationaha.113.004555
32 Bazan, I. S. *et al.* Pulmonary arterial hypertension in the setting of scleroderma is different than in the setting of lupus: A review. *Respiratory medicine* **134**, 42-46 (2018). https://doi.org:10.1016/j.rmed.2017.11.020

33 Hernandez-Sanchez, J. *et al.* Clinical trial protocol for TRANSFORM-UK: A therapeutic open-label study of tocilizumab in the treatment of pulmonary arterial hypertension. *Pulmonary circulation* **8**, 2045893217735820 (2018). https://doi.org:10.1177/2045893217735820

34 Kato, M. & Atsumi, T. Pulmonary arterial hypertension associated with connective tissue diseases: A review focusing on distinctive clinical aspects. *European journal of clinical investigation* (2017). https://doi.org:10.1111/eci.12876

35 Gibbons, E. *et al.* Reversible pulmonary arterial hypertension associated with interferon-beta treatment for multiple sclerosis. *Canadian respiratory journal* **22**, 263-265 (2015).

36 Savale, L., Chaumais, M. C., O'Connell, C., Humbert, M. & Sitbon, O. Interferon-induced pulmonary hypertension: an update. *Current opinion in pulmonary medicine* **22**, 415-420 (2016). https://doi.org:10.1097/mcp.0000000000000307

37 Savale, L., Chaumais, M. C., Sitbon, O. & Humbert, M. Pulmonary arterial hypertension in patients treated with interferon. *The European respiratory journal* **46**, 1851-1853 (2015). https://doi.org:10.1183/13993003.01376-2015

38 Tsuchiya, H. *et al.* Interferon Therapy Exacerbated Pulmonary Hypertension in a Patient with Hepatitis C Virus Infection: Pathogenic Interplay among Multiple Risk Factors. *Internal medicine (Tokyo, Japan)* **56**, 1061-1065 (2017). https://doi.org:10.2169/internalmedicine.56.7822

39 Baechler, E. C. *et al.* Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc Natl Acad Sci U S A* **100**, 2610-2615 (2003). https://doi.org:10.1073/pnas.0337679100

40 Bennett, L. *et al.* Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J Exp Med* **197**, 711-723 (2003). https://doi.org:10.1084/jem.20021553

41 Rice, G. I. *et al.* Assessment of interferon-related biomarkers in Aicardi-Goutieres syndrome associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, and ADAR: a case-control study. *The Lancet. Neurology* **12**, 1159-1169 (2013). https://doi.org:10.1016/s1474-4422(13)70258-8

42 Rice, G. I. *et al.* Assessment of Type I Interferon Signaling in Pediatric Inflammatory Disease. *J Clin Immunol* **37**, 123-132 (2017). https://doi.org:10.1007/s10875-016-0359-1

43 Armangue, T. *et al.* Neonatal detection of Aicardi Goutieres Syndrome by increased C26:0 lysophosphatidylcholine and interferon signature on newborn screening blood spots. *Molecular genetics and metabolism* (2017). https://doi.org:10.1016/j.ymgme.2017.07.006

44 Kim, H. *et al.* Development of a Validated Interferon Score Using NanoString Technology. *Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research* **38**, 171-185 (2018). https://doi.org:10.1089/jir.2017.0127

45 Bjornson, K., Graubert, C. & McLaughlin, J. Test-retest reliability of the gross motor function measure in children with cerebral palsy. *Pediatr Phys Ther* **12**, 200-202 (2000).

46 Ko, J. & Kim, M. Reliability and responsiveness of the gross motor function measure-88 in children with cerebral palsy. *Phys Ther* **93**, 393-400 (2013). https://doi.org:10.2522/ptj.20110374

47 Nordmark, E., Hagglund, G. & Jarnlo, G. B. Reliability of the gross motor function measure in cerebral palsy. *Scand J Rehabil Med* **29**, 25-28 (1997).

48 Salavati, M. *et al.* Reliability of the modified Gross Motor Function Measure-88 (GMFM-88) for children with both Spastic Cerebral Palsy and Cerebral Visual Impairment: A preliminary study. *Res Dev Disabil* **45-46**, 32-48 (2015). https://doi.org:10.1016/j.ridd.2015.07.013

49 Alotaibi, M., Long, T., Kennedy, E. & Bavishi, S. The efficacy of GMFM-88 and GMFM-66 to detect changes in gross motor function in children with cerebral palsy (CP): a literature review. *Disability and rehabilitation* **36**, 617-627 (2014). https://doi.org:10.3109/09638288.2013.805820

50 Palisano, R. J. *et al.* Validation of a model of gross motor function for children with cerebral palsy. *Phys Ther* **80**, 974-985 (2000).

51 Lundkvist Josenby, A., Jarnlo, G. B., Gummesson, C. & Nordmark, E. Longitudinal construct validity of the GMFM-88 total score and goal total score and the GMFM-66 score in a 5-year follow-up study. *Phys Ther* **89**, 342-350 (2009). https://doi.org:10.2522/ptj.20080037

52 Dali, C. I. *et al.* Sulfatide levels correlate with severity of neuropathy in metachromatic leukodystrophy. *Ann Clin Transl Neurol* **2**, 518-533 (2015). https://doi.org:10.1002/acn3.193

53 Malak, R., Kotwicka, M., Krawczyk-Wasielewska, A., Mojs, E. & Samborski, W. Motor skills, cognitive development and balance functions of children with Down syndrome. *Ann Agric Environ Med* **20**, 803-806 (2013).

54 Chen, T. H. *et al.* Randomized, double-blind, placebo-controlled trial of hydroxyurea in spinal muscular atrophy. *Neurology* **75**, 2190-2197 (2010). https://doi.org:10.1212/WNL.0b013e3182020332

55 Adang, L. *et al.* Developmental Outcomes of Aicardi Goutieres Syndrome. *J Child Neurol* **35**, 7-16 (2020). https://doi.org:10.1177/0883073819870944

56 Adang, L. A. *et al.* Development of a neurologic severity scale for Aicardi Goutieres Syndrome. *Mol Genet Metab* **130**, 153-160 (2020). https://doi.org:10.1016/j.ymgme.2020.03.008

57 Bursztejn, A. C. *et al.* Unusual cutaneous features associated with a heterozygous gain-of-function mutation in IFIH1: overlap between Aicardi-Goutieres and Singleton-Merten syndromes. *The British journal of dermatology* **173**, 1505-1513 (2015). https://doi.org:10.1111/bjd.14073

58 Kisla Ekinci, R. M., Balci, S., Bisgin, A., Altintas, D. U. & Yilmaz, M. A homozygote TREX1 mutation in two siblings with different phenotypes: Chilblains and cerebral vasculitis. *European journal of medical genetics* **60**, 690-694 (2017). https://doi.org:10.1016/j.ejmg.2017.09.004

59 Kolivras, A. *et al.* Cutaneous histopathological findings of Aicardi-Goutieres syndrome, overlap with chilblain lupus. *Journal of cutaneous pathology* **35**, 774-778 (2008). https://doi.org:10.1111/j.1600-0560.2007.00900.x

60 Albrecht, J. *et al.* The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol* **125**, 889-894 (2005). https://doi.org:10.1111/j.0022-202X.2005.23889.x

61 Johnson-Huang, L. M. *et al.* A single intradermal injection of IFN-gamma induces an inflammatory state in both non-lesional psoriatic and healthy skin. *J Invest Dermatol* **132**, 1177-1187 (2012). https://doi.org:10.1038/jid.2011.458

62 Krueger, J. *et al.* Tofacitinib attenuates pathologic immune pathways in patients with psoriasis: A randomized phase 2 study. *J Allergy Clin Immunol* **137**, 1079-1090 (2016). https://doi.org:10.1016/j.jaci.2015.12.1318
63 Adang, L. A. *et al.* Hematologic abnormalities in Aicardi Goutieres Syndrome. *Molecular genetics and metabolism* **136**, 324-329 (2022). https://doi.org:10.1016/j.ymgme.2022.06.003
64 Frank, D. B. *et al.* Trends in pediatric pulmonary hypertension-related hospitalizations in the United States from 2000-2009. *Pulmonary circulation* **5**, 339-348 (2015). https://doi.org:10.1086/681226
65 Abman, S. H. *et al.* Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. *Circulation* **132**, 2037-2099 (2015). https://doi.org:10.1161/cir.0000000000000329
66 EM., M. *Mullen Scales of Early Learning*. (American Guidance Service, 1995).
67 Gavazzi, F. *et al.* Reliability of the Telemedicine Application of the Gross Motor Function Measure-88 in Patients With Leukodystrophy. *Pediatr Neurol* **125**, 34-39 (2021). https://doi.org:10.1016/j.pediatrneurol.2021.09.012
68 Paulson, A. & Vargus-Adams, J. Overview of Four Functional Classification Systems Commonly Used in Cerebral Palsy. *Children (Basel, Switzerland)* **4** (2017). https://doi.org:10.3390/children4040030
69 Jolly, M., Kazmi, N., Mikolaitis, R. A., Sequeira, W. & Block, J. A. Validation of the Cutaneous Lupus Disease Area and Severity Index (CLASI) using physician- and patient-assessed health outcome measures. *J Am Acad Dermatol* **68**, 618-623 (2013). https://doi.org:10.1016/j.jaad.2012.08.035
70 Cortes-Hernandez, J., Avila, G., Vilardell-Tarres, M. & Ordi-Ros, J. Efficacy and safety of lenalidomide for refractory cutaneous lupus erythematosus. *Arthritis Res Ther* **14**, R265 (2012). https://doi.org:10.1186/ar4111
71 Khamashta, M. *et al.* Sifalimumab, an anti-interferon-alpha monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* **75**, 1909-1916 (2016). https://doi.org:10.1136/annrheumdis-2015-208562
72 Vashisht, P., Borghoff, K., O'Dell, J. R. & Hearth-Holmes, M. Belimumab for the treatment of recalcitrant cutaneous lupus. *Lupus* **26**, 857-864 (2017). https://doi.org:10.1177/0961203316682097
73 Yokogawa, N., Kato, Y., Sugii, S. & Inada, S. Response to hydroxychloroquine in Japanese patients with systemic lupus erythematosus using the cutaneous lupus erythematosus disease area and severity index (CLASI). *Mod Rheumatol* **22**, 249-255 (2012). https://doi.org:10.1007/s10165-011-0503-y
74 Fitzmaurice, G. M., Laird, N. M., & Ware, J. H. *Applied longitudinal analysis*. (Wiley-Interscience, 2004).
75 Shults, J. *et al.* A comparison of several approaches for choosing between working correlation structures in generalized estimating equation analysis of longitudinal binary data. *Stat Med* **28**, 2338-2355 (2009). https://doi.org:10.1002/sim.3622
76 Shults, J. a. J. M. H. *Quasi-Least Squares Regression*. (Chapman & Hall/CRC, 2014).