Baricitinib in Relapsing Giant Cell Arteritis (GCA): A Phase II, Single-institution, Open-label Pilot Study

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Version	Date	Major Changes
1	25 Oct 2016	Initial protocol
2	03 Nov 2016	Added known evidence of hyperbilirubinemia to exclusions (Sect 7.2), clarified timing of study visit/schedule (Sect 9.6), added required information on study monitoring/auditing plan/inspection/ethical consideration following intraclinic regulatory review
3	25Jul 2017	Removes screening patient global assessment; Excludes Probenecid within 2 weeks of baseline (Sect 7.3), Additional study drug discontinuation criterion (Sect 10.2)
4	21Sept2017	Change to excluded/prior medication (Sect 7.3) to allow patients having been exposed to IL-6 inhibitor to still be considered for study if they were intolerant of the medication and did not have primary failure of the medication for control of GCA. This is in response to increase use of tocilizumab for GCA following FDA approval of tocilizumab for GCA in May 2017
5	28Nov2017	Change to excluded/prior medication (Sect 7.3) to clarify language about prior IL-6 inhibitor use before study entrance Changed tuberculosis screening to include option of different interferon gamma release assay (T-spot test) if initial QuantiFERON-TB Gold test is indeterminate
6	10Jul2018	Changed timing of hepatitis and TB screening. If have had done within the last 6 months for other clinical reason and they were negative without evidence of exposure or symptoms then these negative results will be used for baseline negative and not repeated. This is consistent with clinical practice for patients being treated with biologics. See table 2
7	30Dec2019	Clarification of Exclusion criteria (7.2)

		Clarification for shingles vaccine. At time of initial drafting Zostavax was only option but now Shingrix is available which is okay to have administered while on immunosuppression and would not be exclusion to enrollment and can be done at any time prior to or during study. (7.2.2) Clarification on exclusion language of vision changes. It has been the intent of the investigators that patients not be demonstrating any NEW features of vision loss to prevent this from being a feature of relapse because this is considered a severe relapse and such findings would not be advised to a rapid steroid taper as done in this study protocol. However, it was not the intent of the investigators to exclude patients with prior symptoms of visual ischemia (at time of diagnosis) if they are not having any NEW or worsening vision loss at the time of the documented relapse. We realize that “permanent vision loss” may be misleading if this was present at time of diagnosis (because it will always be present).Language is updated to clarify this point. (7.2.4)

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1. PROTOCOL OVERVIEW

Protocol Title:	Baricitinib in relapsing giant cell arteritis (GCA): a phase II, single-institution, open-label pilot study
Study Chairs:	Kenneth J. Warrington, M.D. – Principal Investigator Matthew J. Koster, M.D. – Co-Principal Investigator
Statistician:	Cynthia Crowson, M.S.
Study Coordinator:	Jane Jaquith, C.C.R.C.
Participating Sites:	Mayo Clinic, Rochester, MN
Activation Date:	1/1/2017
Sample Size:	15
Target Enrollment Period:	60 weeks
Study Design:	Open-label, Phase II
Primary objective:	To determine the safety and tolerability of baricitinib, 4mg oral daily, in GCA
Secondary objective	To gather preliminary data on the efficacy of baricitinib, 4mg oral daily, in patients with relapsing GCA • Relapse-free survival at week 52 • Relapse-free survival at week 24 • Duration of glucocorticoid-free remission • Number of relapses per subject over time • Change from baseline erythrocyte sedimentation rate (ESR) to end of study • Change from baseline C-reactive protein to end of study • Glucocorticoid dose (mg) at week 52 compared to enrollment • Change in BVAS from baseline to end of study

Inclusion criteria	1. Diagnosis of GCA defined by the following Revised GCA Diagnosis Criteria:
	• Age ≥50 years.
	• History of ESR ≥ 50 mm/hour or CRP ≥ 10 mg/L.
	• Presence of at least **one** of the following:
	  ○ Unequivocal cranial symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness, otherwise unexplained mouth or jaw pain upon mastication).
	  ○ Unequivocal symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory stiffness.
	  ○ Systemic inflammatory disease in which the presence of the fever (>38 degrees Celsius for ≥ 7 days), weight loss (> 5 lbs or 10% premorbid weight), and/or night sweats were attributable to GCA and no other cause was

	identified. • Presence of at least **one** of the following: ○ Temporal artery biopsy revealing features of GCA. ○ Evidence of large-vessel vasculitis by angiography or cross-sectional imaging, including but not limited to magnetic resonance angiography (MRA), computed tomography angiography (CTA), positron emission tomography-computed tomography (PET-CT) or evidence of large-vessel or temporal artery vasculitis by ultrasound (US). 2. Relapse with active GCA within 6 weeks of study entry where active disease is defined by an ESR ≥30 mm/hr or CRP ≥10 mg/L AND the presence of at least **one** of the following: • Unequivocal cranial symptoms of GCA (new onset or recurrent localized headache, scalp or temporal artery tenderness, otherwise unexplained mouth or jaw pain upon mastication [i.e., jaw claudication]). • Unequivocal symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory stiffness. • Other feature(s) judged by the clinician investigator to be consistent with GCA or PMR flares (e.g. fever of unknown origin, unexplained weight loss, fatigue/malaise, etc.) 3. Clinically stable at baseline visit (study drug initiation) such that the subject is able to safely participate in the standardized taper regimen in the opinion of the investigator. .

2. STUDY RATIONALE / SPECIFIC AIMS

Giant cell arteritis (GCA) is the most common idiopathic systemic vasculitis in Europe and North America, with an annual incidence of 11-29/100,000 persons ≥ 50 years of age [1-4]. This chronic immune-mediated vasculitis is characterized by inflammation of the medium- and large-sized blood vessels resulting in significant morbidity including blindness, stroke, aortic aneurysm with rupture, and sudden death. GCA affects patients aged 50 years and older and is considered a medical emergency because of the high risk of vision loss, which can occur in up to 15-20% [5, 6].

Glucocorticoids (GC) have remained the mainstay for both induction to remission and maintenance therapy in GCA. Unfortunately, GC contribute substantial toxicity with up to 90% of patients developing significant GC-associated adverse events [7, 8]. Therefore, steroid-sparing agents for both induction and maintenance therapy are greatly needed to decrease treatment associated morbidity. Despite efforts, a steroid-sparing agent with consistent benefit in GCA has not been identified leaving a large unmet need for adjunct immunomodulatory medications in this condition.

Advances in understanding the pathogenesis of GCA has led to developments in potential targeted therapeutics. Recent studies have elucidated the pathogenic role of CD4+ T cells in vasculitic lesions of GCA and two distinct lineages have been identified as key regulators; type 17 helper T cells (Th17) and type 1 helper T cells (Th1) [9]. While Th17 cells appear to be steroid-responsive, Th1 cells appear to be steroid-resistant and likely contribute to ongoing disease activity and late stage complications of the disease. Although biologic agents in GCA are currently under investigation, therapeutics targeting interleukin-6 (tocilizumab and secukinumab) only further block the Th17 pathway with little to no anticipated effect on the pathologic Th1 response.

Baricitinib, an orally administered, potent, selective and reversible inhibitor of JAK1 and JAK2 has shown preliminary safety and efficacy in chronic, immune-mediated inflammatory conditions such as rheumatoid arthritis [14] and psoriasis [11]. This small molecule is uniquely suited as a potential novel therapeutic agent in GCA because of its suppressive effect on both the Th17 (IL-6, IL-23) and Th1 (IL-12, IFN-γ) pathways.

The purpose of this study is to evaluate the safety and tolerability of baricitinib in a population of patients with relapsing GCA. To accomplish this we will perform a single-institution, open-label pilot study assessing the safety and tolerability of baricitinib (4 mg daily, oral, for 52 weeks) in addition to a standardized glucocorticoid taper. It is anticipated that adjunct baricitinib will be safe and well tolerated by patients with GCA and demonstrate preliminary efficacy as measured by reducing inflammatory markers, decreasing steroid requirements and increasing relapse-free survival.

The vasculitis group at Mayo Clinic in Rochester, Minnesota is well-suited for this study with 50 years of GCA research experience accounting for over 200 publications in this condition. In addition, this institution has one of the largest referral and population-based GCA cohorts in North America and has successfully participated in three recent multicenter, international therapeutic clinical trials evaluating biologic agents in patients with GCA.

Primary Objective

To determine the safety and tolerability of adjunct baricitinib (4mg, oral daily, for 52 weeks) in combination with standardized glucocorticoid taper among patients with relapsing GCA.

Secondary Objective

To assess preliminary efficacy of adjunct baricitinib (4mg, oral daily, for 52 weeks) in combination with standardized glucocorticoid taper among patients with relapsing GCA.

3. BACKGROUND/SIGNIFICANCE

3.1. Giant Cell Arteritis

Giant cell arteritis (GCA) is the most common idiopathic systemic vasculitis in persons aged ≥50 years. There is a predilection for vascular inflammation in medium and large arteries with a particular tropism for the proximal aorta and its primary branches. Arterial inflammation leads to narrowing or occlusion from intimal hyperplasia and can have dramatic consequences. Specifically, ischemic cranial symptoms are considered a medical emergency due to the risk of transient or permanent visual loss, which can occur in up to 15-20% of patients with GCA [6, 12]. In addition, patients with GCA are at elevated risk of developing aortic complications (aneurysm, dissection, rupture) which can be associated with significant morbidity and mortality. Indeed, in a population-based study, patients with GCA were 17.3 times more likely to develop thoracic aortic aneurysm [13]. Furthermore, patients with GCA who develop aortic aneurysm and/or dissection have a near 3-fold increased mortality compared to non-GCA patients[14].

3.2. Glucocorticoids

Prompt initiation of high-dose glucocorticoids (GC) remains the cornerstone of treatment of GCA and delay in treatment initiation can increase the risk of severe ischemic complications [15]. Although highly variable, improvement of inflammation can occur within days to weeks, leading to dramatic reduction in inflammatory markers and systemic symptoms. After attaining remission, the GC dose is gradually decreased over a prolonged course of approximately 18-36 months. Nevertheless, within the first year of diagnosis approximately 50% of patients will experience a clinical relapse of the disease despite GC treatment [16]. Furthermore, GC treatment in the affected age-group is associated with a high number of adverse effects (AEs) including, but not limited to, infection, hypertension, diabetes, cataracts, glaucoma and osteoporosis. Such AEs have been reported in up to 90% of patients receiving GC for the treatment of GCA and the risk of AEs increases with the cumulative dose and duration of GC exposure [7, 17]. Therefore, glucocorticoid-sparing agents are greatly needed for both induction and maintenance therapy to decrease the frequency of GC-associated morbidity.

3.3. Glucocorticoid-sparing Agents

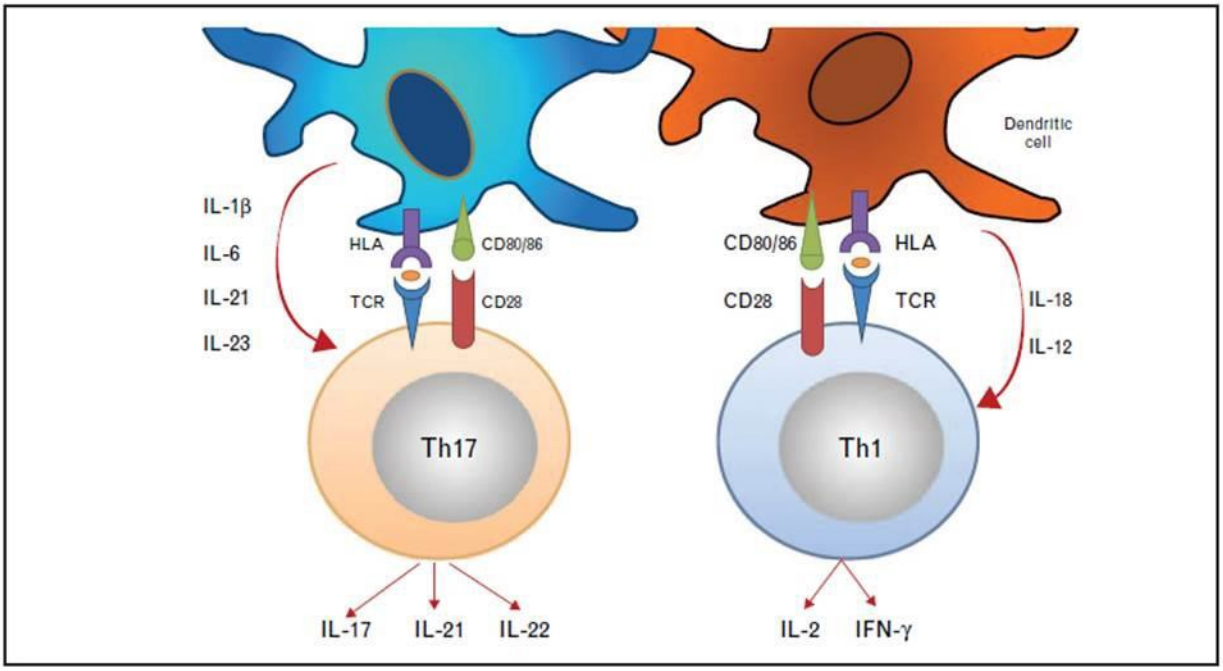
Many investigations have attempted to find a suitable replacement for GC for the treatment of GCA; however, no clear therapeutic agent has shown comparable efficacy or superiority to date. Among conventional immunosuppressive agents, methotrexate has been considered a reasonable second-line agent after GC in patients with severely active/relapsing disease or in patients with high risk for GC-associated adverse events. Nevertheless, small clinical trials evaluating methotrexate in GCA have only found a modest benefit in decreasing relapse risk and glucocorticoid dose reduction [18]. Limited or no benefit has been observed among other oral conventional immunosuppressive agents including leflunomide [19, 20], azathioprine [21] and mycophenolate mofetil [22]. Biologic agents, including tumor necrosis factor alpha inhibitors, have shown equally disappointing results [23-25].

3.4. Immunopathologic Studies

Lymphocytic infiltration in vascular lesions is largely driven by two T cell subsets: T helper type 17 (Th17) and T helper type 1 (Th1) cells [26, 27] (**Figure 1)**. These T cell lineages appear to be stimulated by independent signals from different antigen presenting cells (APC) with Th17 cells requiring interleukin (IL)-1β / IL-6 / IL-21 / IL-23, whereas the Th1 pathway is dependent on APCs secreting IL-12 / IL-18 and interferon gamma (IFN-γ) [27, 28]. In early untreated GCA, both T cell lineages are increased in the peripheral circulation as well as within vascular inflammatory infiltrates. The Th17 pathway appears to be very sensitive to treatment and GC

rapidly control the Th17 effector cytokine production of IL-1, IL-6, IL-17 and IL-23 with concomitant depletion of both circulating and infiltrating Th17 cells [26, 28].

FIGURE 1: Pathophysiology of giant cell arteritis



Despite the effective reduction of the Th17 pathway, a Th1 cell response persists in both biopsy and blood samples of treated patients with GCA [26]. The Th1 cytokine signature (IL-2 and IFN-γ) associated with chronic vasculitis in GCA is poorly susceptible to GC-mediated suppression [28]. Currently, multiple clinical trials investigating biologic agents targeting extracellular proinflammatory cytokines are underway [IL-6, tocilizumab and secukinumab; IL-12/IL-23, ustekinumab; IL-1, gevokizumab]. However, with the exception of ustekinumab, these biologic agents do not impact the Th1 / IL-12 / IFN-γ pathway and therefore may be less likely to exert a greater long-term benefit over GC for suppression of chronic inflammation in GCA mediated by the Th1 cell subset. Results from the small open-label study evaluating ustekinumab have shown initial promise [29]. These preliminary findings may further underscore the importance of blocking aspects of both Th cell lineages involved in the pathogenesis of GCA. To date interruption of the intracellular signaling upregulated by proinflammatory extracellular cytokines has not been pursued in patients with GCA.

Collaborative efforts between the Mayo Clinic vasculitis group and Drs. Cornelia Weyand and Jorg Goronzy have identified the importance of signal transducer and activator of transcription (STAT) transcripts in GCA [30]. Human temporal arteries were implanted in immunodeficient mice and peripheral blood mononuclear cells from patients with GCA were used to reconstitute the murine immune system. In the arterial lesional tissue, STAT-1 transcripts were notably abundant. IFN-γ, the major cytokine inducer of STAT-1, was also 10-fold higher than in age-matched non-GCA controls. Treatment with high-dose dexamethasone reduced IL-6 and IL-1β expression but did not affect Th1 cell accumulation in the vessel wall or decrease IFN-γ production. However, treatment with tofacitinib, a Janus kinase (JAK)/STAT inhibitor, effectively

prevented Th1 cell accumulation in the vessel wall and decreased circulating levels of IFN-γ by 65%. This proof-of-concept study demonstrates that JAK/STAT inhibition can lead to reprogramming of T cell trafficking and prevent T cells from infiltrating the arterial wall, an effect that has not yet been observed with other therapeutic agents in this condition.

3.5. Baricitinib in Autoimmune Disease

Extracellular cytokines bind to cell-surface receptors which then generate downstream signaling through the activation of tyrosine kinases, including JAK. Cytokines induce JAK enzymatic activity by binding to the extracellular portion of their associated receptors, leading to activation of the receptor and initiation of intracellular signaling cascades. STATs, which reside in the cytosol, when stimulated by cytokines bind active phosphorylated receptors and are then in turn phosphorylated by JAKs. This leads to STATs translocating to the nucleus where they bind DNA and activate transcription. Exaggerated, aberrant, or protracted JAK/STAT signaling has been implicated in several autoimmune diseases and therefore provides potential targets for disease modification [31]. Indeed tofacitinib (JAK3 preferential inhibitor) has already been approved for use in rheumatoid arthritis and baricitinib has shown preliminary efficacy in rheumatoid arthritis [32-34], psoriasis [35] and alopecia areata [36].

3.6. Baricitinib in Giant Cell Arteritis

Cytokines and mediators that have been associated with aberrant autoimmunity and increased inflammatory responses in GCA include IL-6, IL-12, IL-23, and interferon γ (IFN-γ). These cytokines signal through the JAK family (JAK1, JAK2, JAK3 and tyrosine kinase 2 [Tyk2]) [37]. Baricitinib is an oral Janus kinase inhibitor with preferential inhibition of JAK1 and JAK2. IL-6 and IFN-γ primarily signal through JAK1 and IL-12 and IL-23 through JAK2. Therefore an agent that preferentially inhibits both JAK1 and JAK2 will provide reduction of intracellular signaling through multiple proinflammatory pathways, reducing activity of both pathologic Th17 and Th1 cell lineages.

Given these findings, an open-label phase II trial of baricitinib in patients with relapsing GCA is proposed. The purpose of this study will be to evaluate the safety and preliminary efficacy of baricitinib in treatment of patients with relapsing GCA.

4. OBJECTIVE(S) and ENDPOINT(S)

Objectives	Endpoints/Measures
Primary	
• To investigate the safety of baricitinib, 4 mg oral daily for duration of 52 weeks, administered to patients with relapsing GCA in combination with a standardized glucocorticoid taper	• Incidence of adverse effects and serious adverse effects, changes in hematology and clinical chemistry patterns
Secondary	
• To evaluate preliminary efficacy of baricitinib, 4 mg oral daily for duration of 52 weeks, administered to patients with relapsing GCA in combination with a standardized glucocorticoid taper	• Relapse-free survival at week 52 • Relapse-free survival at week 24 • Duration of glucocorticoid-free remission

	• Duration of glucocorticoid-free remission • Number of relapses per subject over time • Change from baseline erythrocyte sedimentation rate to end of study • Change from baseline C-reactive protein to end of study • Glucocorticoid dose (mg) at week 52 compared to baseline • Change in BVAS from baseline to end of study

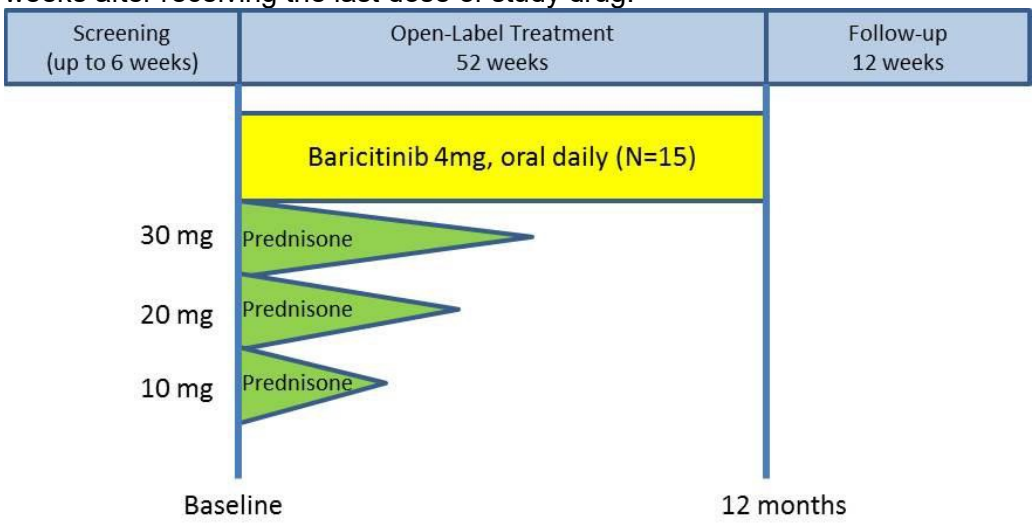
5. STUDY DESIGN

5.1.1. Study Definitions

- *Active Disease*: ongoing signs or symptoms attributable to GCA accompanied by an elevated ESR ≥ 30 mm/hour or CRP 10 mg/L.
- *Clinically stable:* improvement in or absence of ongoing signs or symptoms attributable to GCA as evidenced by reduction in symptoms and/or improvement in (or normalization of) inflammatory markers
- *Relapse*: the recurrence of signs or symptoms (i.e. active disease) attributable to GCA in subject previously in remission
- *Remission*: the absence of signs or symptoms attributable to GCA and normalization of erythrocyte sedimentation rate (<30 mm/hour) and C-reactive protein (<10 mg/L).
- *Glucocorticoid-free remission*: the absence of signs or symptoms attributable to GCA following discontinuation of glucocorticoids
- *Signs and symptoms of GCA*: fronto-temporal headache; scalp tenderness; abnormality of temporal artery (tenderness, nodularity, decreased pulse); jaw, arm or leg claudication; polymyalgia rheumatica; vision change (blurring, diplopia); transient (amaurosis fugax) or permanent vision loss.

5.1.2. Design Overview

- A screening phase of up to 6 weeks in duration
- 52-week open-label study drug treatment phase with standardized prednisone taper
- A 12-week follow-up phase to ensure that all subjects are evaluated for safety at 12 weeks after receiving the last dose of study drug.



5.2. Study Design and Methods

This open-label, single-center pilot study will enroll and treat 15 subjects with relapsing GCA. All subjects will receive oral baricitinib 4 mg daily for a duration of 12 months. All patients with GCA enrolled will have undergone a recent relapse within 6 weeks prior to study entry. In response to the observed relapse, prednisone will be re-instituted (for patients who have previously tapered off glucocorticoids) or increased (for patients currently on glucocorticoids) based on the level of glucocorticoid treatment the patient was on when the relapse occurred, as further outlined below.

Subjects with evidence of relapse will be recruited from the clinical practice of Mayo Clinic Rheumatology. If initial inclusion criteria are met, the subject will be consented and begin screening for study enrollment. The screening period may be as short as 2 weeks or as long as 6 weeks. During the screening period, treating physicians may increase prednisone in the following manner: if relapse occurred with prednisone doses ≥ 20 but <30 mg/day, an increase to at least 30 mg/day (but not to exceed 40 mg/day) will occur. For those with relapse present with prednisone dose ≥10 but <20 mg/day an increase to at least 20 mg/day (but not to exceed 30 mg/day) will occur. For those with relapse occurring with prednisone from 0 to <10 mg/day, a reinstitution or increase to at least 10 mg/day (but not exceeding 20 mg) will occur. This increase will occur during the screening phase following informed consent. The prednisone increase is in response to the observed relapse, in keeping with standard clinical practice.

To be enrolled, subjects must have clinically stable disease and treated with a prednisone dose of either 30 mg, 20 mg, or 10 mg (in accordance with their respective entry tier) for a minimum of 2 weeks before initiation of study drug and standardized taper. As such, the patient is not, by the physician's clinical assessment, showing signs of worsening disease (new symptoms or increasing severity of the symptoms that were observed at time of relapse) attributable to GCA. For example, a patient with relapse occurring at 30 mg prednisone may be increased to 40 mg/day for 2 weeks, 35 mg/day for 2 weeks and then 30 mg/day for two weeks. If deemed clinically stable on 30 mg/day prednisone after two weeks, the subject may enroll and begin study drug and standardized glucocorticoid taper. Additional examples: 1) if a relapse occurred at 15 mg/day, a patient may be increased to 20 mg for 2 weeks and if deemed clinically stable may undergo initiation of study drug after being on 20 mg for 2 weeks; 2) if a patient has previously been able to discontinue prednisone therapy and has a clinical relapse, prednisone can be re-initiated at 10 mg/day and if clinically stable at 2 weeks may proceed to enrollment Once enrolled, subjects will begin study drug and reduce their prednisone dose on a standardized tapering schedule according to their respective entry dose (30 mg, 20 mg, 10 mg), as outlined in **Table 1**.

If a relapse occurs during the standardized taper (without evidence of severe ischemic event: defined as stroke, vision loss, critical limb ischemia) the patient will be removed from the standardized prednisone taper regimen but continue study drug for the remaining balance of the 52-week study period, provided no contraindication or criteria for study drug withdrawal is present at time of relapse. Once removed from the standardized prednisone taper, subsequent prednisone dose and management will be at the discretion of the treating provider. If a second relapse occurs, or if a relapse with the accompaniment of an aforementioned severe ischemic event is observed, then the study drug will be discontinued and prednisone and/or other alternative treatments will be provided as directed and at the discretion of the treating provider.

Safety and efficacy data will be collected at the time of each clinical visit. In the absence of disease worsening, relapse, or drug toxicity, subjects will continue baricitinib for 52 weeks. Following completion of 52 weeks of treatment, all subjects will discontinue baricitinib. For safety purposes a follow-up visit will occur 12 weeks after discontinuation of the study drug for all

subjects, including those with earlier study drug withdrawal.
The maximum duration of subject participation (including screening) is 70 weeks. Completion of the study is defined as completion of the 52-week treatment period and 12-week follow-up visit.

TABLE 1: Standardized prednisone taper

Time (Week)	Prednisone dose and tapering schedule		
Screening: -6 to -2*	30	20	10
0	30	20	10
1	25	17.5	9
2	22.5	15	8
3	20	12.5	7
4	17.5	10	6
5	15	9	5
6	12.5	8	5
7	10	7	4
8	9	6	4
9	8	5	3
10	7	5	3
11	6	4	2
12	5	4	2
13	5	3	1
14	4	3	1
15	4	2	0
16	3	2	
17	3	1	
18	2	1	
19	2	0	
20	1		
21	1		
22	0		
*subjects must be on stable dose of either 30 mg, 20 mg, or 10 mg for 2 weeks prior to baseline (week 0)			

5.3. Treatment Arms and Duration

This is an open-label, single-arm study. All subjects will receive the study drug for a maximum of 52 weeks in combination with a standardized prednisone taper.

5.4. Type and Number of Subjects

The study population will be comprised of 15 subjects with GCA who have experienced a relapse, determined by demonstrating active disease, within 6 weeks of baseline. Active disease will be defined as showing evidence of signs or symptoms attributable to GCA and the presence of either an ESR ≥ 30 mm/hr or a CRP ≥ 10 mg/L. Subjects demonstrating symptoms of visual manifestations (i.e. double vision, transient or permanent partial/complete vision loss), cerebrovascular compromise (ischemic stroke deemed secondary to GCA), or limb ischemia will be ineligible for enrollment. Patients on glucocorticoids for ≥ 4 years consecutively (without interruption of more than 1 month) will be excluded to avoid issues with precipitating secondary adrenal insufficiency and/or symptoms of steroid withdrawal from an accelerated standardized glucocorticoid taper.

5.5. Design Justification

This is a single-center, open-label study to evaluate the safety of baricitinib in GCA and to develop preliminary evidence of efficacy to support the potential conduct of a larger randomized trial.

The design of this study is similar in to other open-label phase II studies evaluating biologic medications in subjects with GCA [29, 38].

Glucocorticoids represent the only current standard of care treatment for patients with GCA. As such, prednisone will be continued during the initiation of the study drug. Subjects will enter the study at one of three doses of prednisone (30 mg, 20 mg, or 10 mg). Subjects should be on a stable prednisone dose for a minimum of 2 weeks (maximum 6 weeks) prior to initiation of study drug. Following study drug initiation prednisone tapering will occur in a standardized manner.

The 52-week study duration was chosen to assess for safety of medication use as well as to observe preliminary evidence of efficacy based on duration of glucocorticoid-free remission and relapse-free survival.

5.6 Dose Justification

5.6.1. Baricitinib

Subjects will receive a fixed dose of baricitinib, 4 mg oral daily, for duration of 52 weeks. The dose of baricitinib will remain constant throughout the study. If serious adverse events occur related to the study medication, the dose will not be decreased rather the study drug will be withdrawn.

5.6.2. Justification of Trial Dose

Baricitinib doses of 1 mg, 2mg, 4 mg, and 8 mg have been investigated in subjects with rheumatoid arthritis. Doses ≤4 mg have shown efficacy in rheumatoid arthritis with adverse event rates similar to placebo. However, adverse event rates have been noticed to be higher in subject groups receiving 8 mg [32-34, 39].

5.6.3. Glucocorticoids (prednisone)

Glucocorticoids are considered by consensus expert opinion to be the only class of medications that has shown consistent efficacy in GCA and are considered standard of care. As such all subjects will receive background prednisone at time of enrollment and then undergo standardized taper.

5.6.4. Justification of Glucocorticoid Taper

Consensus guidelines recommend an increase in glucocorticoid treatment at the time of relapse to a previous higher dose, followed by repeat attempts at tapering once symptoms have improved/stabilized [40]. The protocol standardized tapering regimen is expedited compared to clinical practice in order to assess preliminary efficacy of the study drug.

Study subjects may enter the standardized taper at one of three levels; 30 mg, 20 mg or 10 mg. These strata were specifically designed to allow for appropriate increase of GC in response to the relapsing disease in a manner proportional to the dose of GC the subject was on at the time of relapse. It is common practice in treating relapses to increase GC to a prior dose in which the subject was asymptomatic. As such the three tier strata allows for clinicians to increase GC appropriately to achieve symptomatic control prior to a standardized taper instead of mandating

an increase to a required entry dose regardless of the GC dose at time of relapse. For example, it would be considered unnecessary, in the majority of circumstances, to increase a patient from 5 mg/day of prednisone to 30 mg/day for a moderate relapse of PMR symptoms, however an increase to 10 mg/day would be reasonable.

6. BENEFIT:RISK ASSESSMENT

6.1. Benefit Assessment

The efficacy of baricitinib in subjects with GCA has not yet been established. However, available pre-clinical data provide rationale for the use of JAK inhibitors in GCA. Furthermore, baricitinib has been shown to be safe and effective in patients with rheumatoid arthritis. Glucocorticoids are the current standard of care treatment for GCA. However, prolonged use with GCs is associated with significant risk of adverse events. This study, if successful, will provide preliminary evidence that may result in a new therapy for GCA where there remains a clear unmet need.

Subjects will be receiving standard of care treatment with GC during the study period, albeit with a quicker taper than is typically followed in clinical practice. Subjects will receive high level of care throughout the study and will benefit from the frequent physical examinations and frequent monitoring of vital signs and blood tests.

6.2. Risk Assessment

There are currently no known contraindications or identified risks requiring special warnings or special precautions for use of Baricitinib. Potential risks have been identified and are detailed in the included accompanying Investigator Brochure for Baricitinib (LY3009104). Potential risks are summarized below.

Increased Adverse Events Due to Increased Exposures in Patients with Renal Impairment:
Data from completed studies indicate that subjects with renal impairment have increased exposure to baricitinib. Increased exposure could place a person at increased risk for any other risk that is related to exposure. Investigators will follow dosing guidelines specified in the protocol, and monitor creatinine in study subjects and follow protocol drug interruption and discontinuation criteria.

Myelosuppression: Baricitinib is anticipated to down-regulate the JAK pathway and result in changes to white blood cell counts. Although dose-related decreases in neutrophils and other phagocytic cell lines have been observed, neutropenia and lymphocytopenia have been observed infrequently. Investigators will monitor leukocyte parameters in study subjects and follow protocol drug interruption and discontinuation criteria.

Increased Infections (including opportunistic infections and herpes zoster): In addition to the observed decreases in phagocytic cells, JAK inhibition down-regulates cytokines related to the immune system. Although infections and infestations were the most frequently reported treatment emergent adverse event (TEAE) occurrence of infections typically considered to be opportunistic has not been observed in clinical studies with baricitinib. The incidence rate of herpes zoster observed in baricitinib studies is within the range reported in observational studies and clinical trials of patients with RA. Investigators will monitor subjects for clinical signs and symptoms of infectious events, including herpes zoster. If a subject is clinically diagnosed with herpes zoster, the investigator will interrupt investigational product, initiate standard of care

(including antiviral therapy and relevant supportive care as appropriate), monitor for multi-dermatomal involvement or other evidence of dissemination, and follow subjects until clinical recovery of skin lesions (vesicles).

Increased Cardiovascular Events Due to Changes in Lipids: Increases in mean total cholesterol, LDL, HDL, and triglycerides have been noted in studies with baricitinib. Nuclear magnetic resonance data indicate that the changes in cholesterol are due primarily to increases in the number of HDL particles without a change in HDL particle size; an increase in the number of large LDL particles with no significant increases in small, medium-small or very small LDL particles; and an increase in the number of total, as well as medium and small, very low density lipoprotein particles. The mean values for the HDL/LDL ratio did not change. These changes in lipid particles, particularly in view of the observed increase in large LDL particles, suggest that the overall effect on the vasculature may not be atherogenic Any increase in cholesterol carries a potential risk of cardiovascular events. Data from patients with rheumatoid arthritis given 4 to 15 mg baricitinib QD or 5 mg baricitinib BID have shown no clinically meaningful changes in vital signs or ECG parameters for baricitinib versus placebo. Investigators will monitor for change in lipid profile from baseline to week 16 to assess for the development of hyperlipidemia. If present then institution of hyperlipidemia medications will be suggested if clinically recommended.

Fetal Malformations: Reproductive toxicity was observed in rat and rabbit toxicology studies, including maternal toxicity and skeletal malformations in the rat fetus. A decrease in mating performance (fertility and copulation indices) was observed in the male rat fertility study. This change occurred without effects on spermatogenesis as assessed by histopathology and semen/sperm endpoints. Pregnant women will not participate in this study. To manage risks, women of reproductive potential should avoid becoming pregnant by using 2 forms of highly effective contraceptives while participating in clinical studies and for 28 days following exposure to baricitinib. Screening for pregnancy will occur during the screening period and at all study visits. The population affected by GCA has an average diagnosis age of 72, therefore the likelihood of patients being of childbearing age is of low likelihood.

Emergence of Malignancies Previously Contained by the Immune System: Baricitinib has immunomodulatory effects on the immune system. Effects on the immune system may permit emergence of malignancies previously contained by the immune system. No signals concerning effects of baricitinib on malignancy have emerged from clinical studies. Patients should be monitored closely for evidence of neoplasia or malignancy, and study drug should be discontinued if such events occur.

Accelerated Prednisone Taper: In addition to the information available for Baricitinib, a quicker taper of steroids may lead to withdrawal side effects. Subjects may experience GCA relapse during steroid taper. Inclusion of subjects with stable disease on study entry who are able to safely participate in the steroid taper and have had duration of steroids ≤ 4 years. Monitoring of subjects during steroid taper and following discontinuation. Subjects with severe ischemic manifestations related to GCA will be excluded from the trial. Disease relapses will be treated with increased dose of GCs.

6.3. Overall Benefit:Risk Conclusion

While the efficacy of baricitinib in subjects with GCA is unknown, pathophysiologic rationale exists to consider use in GCA, given that baricitinib has been shown to be safe and effective in rheumatoid arthritis.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with baricitinib are justified by the anticipated benefits that may be afforded to subjects with GCA. If baricitinib is able to sustain a GC-free remission this would significantly reduce the burden of GC-related toxicity, which is commonly encountered in long term management of subjects with GCA.

7. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

7.1 Inclusion Criteria

Subjects are eligible for enrollment in the study if the following inclusion criteria are met:

1. Diagnosis of GCA defined by the following Revised GCA Diagnosis Criteria:
   - Age ≥50 years.
   - History of ESR ≥ 50 mm/hour or CRP ≥ 10 mg/L.
   - Presence of at least **one** of the following:
     - Unequivocal cranial symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness, otherwise unexplained mouth or jaw pain upon mastication).
     - Unequivocal symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory stiffness.
     - Systemic inflammatory disease in which the presence of the fever (>38 degrees Celsius for ≥ 7 days), weight loss (> 5 lbs or 10% premorbid weight), and/or night sweats were attributable to GCA and no other cause was identified.
   - Presence of at least **one** of the following:
     - Temporal artery biopsy revealing features of GCA.
     - Evidence of large-vessel vasculitis by angiography or cross-sectional imaging, including but not limited to magnetic resonance angiography (MRA), computed tomography angiography (CTA), positron emission tomography-computed tomography (PET-CT) or evidence of large-vessel or temporal artery vasculitis by ultrasound (US).

2. Relapse with active GCA within 6 weeks of study entry where active disease is defined by an ESR ≥30 mm/hr or CRP ≥10 mg/L AND the presence of at least **one** of the following:
   - Unequivocal cranial symptoms of GCA (new onset or recurrent localized headache, scalp or temporal artery tenderness, otherwise unexplained mouth or jaw pain upon mastication [i.e., jaw claudication]).
   - Unequivocal symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory stiffness.
   - Other feature(s) judged by the clinician investigator to be consistent with GCA or PMR flares (e.g. fever of unknown origin, weight loss, fatigue/malaise, etc.)

3. Clinically stable at baseline visit (study drug initiation) such that the subject is able to safely participate in the standardized taper regimen in the opinion of the investigator.

7.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Presence of any other autoimmune disease (such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory arthritis, other vasculitides, scleroderma, polymyositis, dermatomyositis, or other similar systemic connective tissue diseases).
2. Subjects demonstrating symptoms of active or newly developing visual loss (transient or permanent blindness) or diplopia attributable to GCA at the time of relapse. Patients with history of visual ischemia present at the time of original GCA diagnosis will still be considered eligible if at the time of the documented pre-study relapse there is no evidence of change/progression of their known visual deficit that can be attributed to active GCA.
3. Subjects with history of aortic dissection, myocardial infarction, or cerebrovascular attack attributable to GCA.
4. Has received, or is expected to receive, any live virus vaccinations (with the exception of herpes zoster vaccination) within 3 months before the first dose of study drug, during the study, or within 3 months after the last administration of the study drug. All patients who have not received the herpes zoster vaccine at screening will be encouraged (per local guidelines) to do so prior to randomization; vaccination must occur >4 weeks prior to randomization and start of investigational product. Patients will be excluded if they were exposed to herpes zoster (Zostavax) vaccination within 4 weeks of planned randomization. Patients may receive the inactivated (non-live) herpes zoster vaccine (Shingrix) at any time prior to or after the study start.
5. Organ transplant recipients.
6. Have had a major surgery within 8 weeks prior to screening or will require major surgery during the study that, in the opinion of the investigator would pose an unacceptable risk to the patient.
7. Have experienced any of the following within 12 weeks of screening: myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage IV heart failure
8. Have a history or presence of cardiovascular (including but not limited to uncontrolled hypertension), respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, or neuropsychiatric disorders, or any other serious and/or unstable illness that, in the opinion of the investigator, could constitute an unacceptable risk when taking investigational product or interfere with the interpretation of data.
9. Are largely or wholly incapacitated permitting little or no self-care, such as being bedridden or confined to a wheelchair.
10. Have an estimated glomerular filtration rate (eGFR) of <50 mL/min/1.73 m².
11. Have a known history of chronic liver disease with the most recent available aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal (>2 x ULN)
12. Known evidence of hyperbilirubinemia with a prior total bilirubin ≥1.5 x ULN.
13. Have a history of lymphoproliferative disease; or have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; or have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for < 5 years.
    a. Subjects with uterine cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease for at least 3 years may participate in the study
    b. Subjects with basal cell or squamous epithelial skin cancers which have been completely resected with no evidence of recurrence for at least 3 years may participate in the study.
14. Active infections, or history of recurrent infections or have required management of acute or chronic infections as evidenced by any of the following:

a. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, cytomegalovirus, herpes simplex, herpes zoster, or atypical mycobacteria).
b. History or suspicion of chronic infection (e.g. prosthetic joint infection)
c. Hospitalization for treatment of infection within 60 days of baseline visit
d. Use of parenteral (IV or IM) antimicrobials (antibacterial, antifungals, antivirals, or antiparasitic agents) within 60 days of baseline or oral antimicrobials within 30 days of baseline visit for treatment of an active infection. This does not include the use of antibiotics for prophylaxis against pneumocystis pneumonia since this is considered standard of care for patients on prednisone ≥ 20 mg/day for longer than 3 consecutive months.

15. Have had symptomatic herpes zoster infection within 12 weeks prior to screening.
16. Have a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster or CNS involvement)
17. In the opinion of the investigator, are at an unacceptable risk for participating in the study.
18. Have known or documented diagnosis of human immunodeficiency virus (HIV).
19. Have known or documented primary immunodeficiency.
20. Have had household contact with a person with active tuberculosis (TB) and did not receive appropriate and documented prophylaxis for TB.
21. Have had evidence of active TB or have previously had evidence of active TB and did not receive appropriate and documented treatment.
22. Have evidence of latent TB as documented by a local lab positive QuantiFERON®-TB Gold test and a normal chest x-ray, unless a patient completes at least 4 weeks of appropriate treatment prior to study entry and agrees to complete the remainder of treatment while in the trial.
    a. If the QuantiFERON®-TB Gold test results are positive, the patient will be considered to have latent TB and will be excluded, unless treatment is initiated as outlined above. If the test is indeterminate, the test may be repeated once within 2 weeks of the initial value with either a second QuantiFERON®-TB Gold Test or with a different interferon gamma release assay (i.e. T-Spot tuberculosis test).. If the second test result is again not negative (i.e. positive or indeterminate), the subject will be considered to have latent TB (for purposes of this study) and will be excluded, unless treatment is initiated as outlined above.
    b. Exceptions include subjects with a history of active or latent TB who have documented evidence of appropriate treatment and with no history of re-exposure since their treatment was completed. (Such subjects would not be required to undergo the protocol specific TB testing, but would require a baseline chest x-ray).
23. Have a positive test for HBV defined as:
    a. Positive for hepatitis B surface antigen (HBsAg), or
    b. Positive for anti-hepatitis B core antibody (HBcAb)

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

24. Have HCV (positive for anti-hepatitis C antibody with confirmed presence of HCV).
25. Have any of the following specific abnormalities at time of relapse or during screening:
    a. ALT or AST > 2 x ULN
    b. Hemoglobin < 10 g/dL
    c. Total white blood cell count (WBC) < 2500 cells/μL)
    d. Neutropenia (absolute neutrophil count [ANC] < 1200 cells/μL
    e. Lymphopenia (lymphocyte count < 750 cells/μL)
    f. Thrombocytopenia (platelets < 100,000 cells/μL)
    g. eGFR < 50 mL/min/1.73m²

    In the case of any of the aforementioned laboratory abnormalities, the tests may be repeated once within approximately 2 weeks from the initial values, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility

criterion.

26. Are pregnant or breast feeding at the time of screening or enrollment.
27. Are females of childbearing potential who do not agree to use 2 forms of highly effective birth control when engaging in sexual intercourse with a male partner while enrolled in the study and for at least 4 weeks following the last dose of the study drug
    a. Females of non-childbearing potential are defined as women ≥60 years of age, women ≥40 but <60 years of age what had had cessation of menses for at least 12 months, or whom who are congenitally or surgically sterile (that is have had a hysterectomy, or bilateral oophorectomy or tubal ligation)
    b. The following birth control methods are considered highly effective (the subject should choose 2 to be used with their male partner
        i. Oral, injectable, or implanted hormonal contraceptives
        ii. Condom with spermicidal foam, gel film, cream or suppository
        iii. Occlusive cap (diaphragm or cervical/vault caps) with a spermicidal foam, gel, film, cream or suppository
        iv. . Intrauterine device
        v. Intrauterine system (for example progestin-releasing coil)
        vi. Vasectomies male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
28. Are males who do not agree to use 2 forms of highly effective birth control (see above) while engaging in sexual intercourse with females partners of childbearing potential while enrolled in the study and for 4 weeks after the last dose of the study drug.
29. Have donated more than a single unit of blood within 4 weeks prior to screening or intend to donate blood during the course of the study.
30. Have a history of chronic alcohol abuse, IV drug abuse, or other illicit drug above within the 2 years prior to screening.
31. Have previously received baricitinib for other investigational study.
32. Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures
33. Are currently enrolled in, or discontinued within 4 weeks prior to screening from any other clinical trial involving an investigational product or nonapproved use of a drug or device or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
34. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling whether biological or legally adopted.
35. Have a chronic medical illness requiring the use of oral of IV glucocorticoid treatment (e.g. asthma or emphysema) during the trial or requiring long term glucocorticoid treatment such that they would not be able to safely undergone a standardized glucocorticoid taper.

7.3. Excluded Prior/Concomitant Therapy

Had prior treatment with any of the following:

- Systemic immunosuppressives, including azathioprine, oral cyclosporine A, tacrolimus, mycophenolate mofetil and IL-1ra (anakinra) within 4 weeks of baseline.
- Leflunomide within 12 weeks of baseline
- Methotrexate within 2 weeks of baseline
- Etanercept within 4 weeks or within 8 weeks of baseline with adalimumab, certolizumab, golimumab, infliximab
- Cyclophosphamide within 8 weeks of baseline

- Received any anti-IL6 agent (tocilizumab, sirukumab, sarilumab) and had failure to control GCA symptoms (i.e. primary therapeutic failure) at any point prior to study screening/entry.
    - Patients having received an anti-IL6 agent that were intolerant to the medication (e.g. injection site or infusion reaction) may still be considered eligible for study enrollment.
    - Patients for which an IL-6 agent is being stopped for reason other than therapeutic failure are also considered eligible for study enrollment.
    - Prior to baseline visit/study drug initiation, the patient must be off of the anti-IL6 agent for 4 weeks prior to baseline for infusible (intravenous) formulations and 2 weeks prior for subcutaneously administered formulations.
- Rituximab within 12 months of baseline or longer if B cell counts have not returned to normal range or baseline levels
- Abatacept within 8 weeks of baseline
- Tofacitinib at any point prior to study screening/entry
- Intravenous (pulse) doses of glucocorticoid defined as methylprednisolone > 100 mg/day within 8 weeks of baseline
- Probenecid within 2 weeks of baseline visit

8. STUDY TREATMENT

8.1 Investigational Product

	Study Treatment
Product name	Baricitinib
Dosage form	Tablet
Unit dose	4 mg
Route of administration	Oral
Dosing instruction	Daily

The term “study drug” and “study treatment” are used throughout the protocol to describe the investigational product received by the subject per protocol design (i.e. barcitinib 4 mg oral tablet).

Baricitinib will be supplied by Eli Lilly [investigational product (IP) manufacturer]. The tablets are composed of baricitinib free base and the inactive ingredients microcrystalline cellulose, mannitol, croscarmellose sodium and magnesium stearate. Each tablet contains baricitinib equivalent to 4 mg of the free base compound. The supplied tablets will be held at the Mayo Clinic Outpatient Research Pharmacy during the duration of the study and dispensed to the patient at each scheduled visit with sufficient doses until the subsequent scheduled visit. The maximum amount of supply provided will be 2 months. The medication will be stored according to specification on the label. Patients will keep a diary of all days on which baricitinib is taken to assess compliance at each study visit.

9. STUDY PROCEDURES

9.1. Recruitment

Recruitment will occur through the clinical practices of the investigators at the study site. Subject enrollment at the study site will not occur until Institutional Review Board (IRB) approval of this protocol and the informed consent form (ICF) has been obtained. Details of the goals of the research and the risk and benefits of the protocol will be reviewed with each potential study subject. Recruitment will occur by physicians or study coordinators.

Subjects who decline participation will continue to be followed by their current physician as deemed appropriate.

9.2. Screening

This research study will be explained in lay language to each potential research subject. The subject will sign an informed consent form before undergoing any screening investigations (including labs). The screening period will last for a minimum of two weeks and a maximum of six weeks.

9.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the trial but are not enrolled or do not receive study drug. In order to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities, a minimal set of screen failure information will be collected and retained including demographics, screen failure details and eligibility criteria.

Subjects who are not able to achieve a clinically stable dose (as outlined in the tiered entry description), for a minimum of two weeks during the screening period will be considered screen failures.It is anticipated that for each patient enrolled, 2-3 subjects will need to be screened. Therefore, it is expected that 30-45 patients will be screened in order to enroll 15 patients.

9.4. Retesting

If the subject has signed the Informed Consent Form (ICF) and failed to meet at least one entry criterion, the site may retest laboratory values once during the screening period. Laboratory parameters can only be re-tested once. If a different laboratory parameter is found to be out of range in the re-test, no further testing is allowed and the patient will be ineligible. Re-testing may be performed to determine eligibility within the screening window. Subjects that have laboratory values that do not meet the entry criteria following the re-test are deemed a screen failure. A Quantiferon-TB® test can only be repeated once if initial is indeterminate. If second test is indeterminate or positive then the subject is considered a screen failure.

9.5. Enrollment

Women: GCA occurs more commonly in women than men (approximate 2:1 ratio) and as such it is anticipated that more women will be enrolled than men.
Pregnant women: Pregnant women are excluded from this study.
Pediatric Subjects: GCA, by classification, occurs in subjects aged ≥ 50 years of age. As such pediatric subjects are not included in this study.
*Underrepresented Ethnic/Racial Minorities:*GCA has been reported to occur in most ethnicities; however, it is most common in Caucasians. There will be no exclusion of any subject based on sex, ethnicity, race, or socioeconomic status.

9.6. Visit Frequency/Visit Schedule

Subjects will be evaluated for potential eligibility. Once eligibility is deemed likely, they will be consented and undergo screening. Labs pertaining to determination of eligibility will be obtained during the screening period [QuantiFERON-TB, Hepatitis panel, pregnancy test (if applicable)]. If standard of care labs (complete blood count, inflammatory markers, creatinine, transaminases) were performed at time of observed relapse these will be used for assessment of their respective eligibility laboratory parameters. If they were not drawn at time of observed relapse they will be drawn during the screening period. Standard of care labs will be obtained at each follow up visit, including the 12-week post treatment visit (W64).Lipid profiles will be obtained at week 0 and week 16.

Imaging can be performed in the study period with non-invasive angiography if clinically indicated and is

not considered a requirement for screening or necessary for study enrollment. Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) is recommended at time of diagnosis for patients with GCA (level of evidence Class I, Level C) [41]. If large vessel involvement is observed on advanced imaging, follow up scan at 12-15 months is recommended.

Upon enrollment (Week 0), the study drug will be initiated and standardized GC taper begun. A follow-up visit will occur at week 4 (W4), week 8 (W8), then every 8 weeks until week 52 (W52) when study drug will be discontinued. After study drug is completed a 12-week follow up visit will occur (W64).

Visit dates can by ±4 days from the assigned week to allow for subject travel and investigator availability. A summary of the visit schedule can be seen in the **Table 2**.

Table 2: Visit Schedule

Study Date W=Week (±4 days)	Observed Relapse	Screening (up to 42 days)	W0	W4	W8	W16	W24	W32	W40	W52	W64
Study drug initiation			X								
Prednisone taper initiation			X								
Office visit	X		X	X	X	X	X	X	X	X	X
Data Forms											
Informed consent	X										
Eligibility review	X	X	X								
Demographics		X									
Baseline medical history		X									
Medications		X									
Tobacco use		X									
Patient Global Assessment			X	X	X	X	X	X	X	X	X
Physician Global Assessment			X	X	X	X	X	X	X	X	X
Vascular Damage Index			X							X	
Birmingham Vasculitis Activity Score			X	X	X	X	X	X	X	X	X
Imaging											
CTA or MRA Chest[a]		X									
Labs											
Hepatitis panel[b]		X*									
Tuberculosis test (Quantiferon-TB or T-spot TB)		X*									
Lipid profile			X			X					
Pregnancy test[c]		X	X	X	X	X	X	X	X	X	X
CBC w/diff	X		X	X	X	X	X	X	X	X	X
ESR	X		X	X	X	X	X	X	X	X	X
CRP	X		X	X	X	X	X	X	X	X	X
ALT	X		X	X	X	X	X	X	X	X	X
Creatinine w/EGFR	X		X	X	X	X	X	X	X	X	X
As necessary											
Hospitalization		X	X	X	X	X	X	X	X	X	X
Adverse event report		X	X	X	X	X	X	X	X	X	X
Death		X	X	X	X	X	X	X	X	X	X
Protocol deviation		X	X	X	X	X	X	X	X	X	X
Study therapy discontinuation		X	X	X	X	X	X	X	X	X	X

[a] Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) at physician discretion if has not had previously or at baseline of diagnosis. If large vessel involvement observed on advanced imaging, follow up scan at 12-15 months is recommended. These imaging studies are not part of protocol screening requirements and are considered standard of care (Class I, Level C) [41].

[b] Hepatitis panel consists of the following: Hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antibody (anti-HBs), anti-hepatitis B core antibody (anti-HBc) total, and anti- hepatitis C (anti-HCV).

[c] For women of child bearing potential. Subjects of non-child bearing potential as defined in exclusion criteria are exempt from pregnancy screening.

*For patients with hepatitis panel and/or tuberculosis testing (Quantiferon-TB or T-Spot TB test) performed within 6 months prior to study entry screening for other clinical purpose, if these tests were confirmed negative and the patient has had no known exposure to either hepatitis or tuberculosis and the patient demonstrates no clinical symptomatology suggestive of these conditions then the prior negative result (within the aforementioned time frame) will be considered as their baseline negative evaluation and repeat testing for these conditions during the screening period is not required.

9.7. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the case report form) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria.

9.8. Efficacy

Efficacy of baricitinib in GCA will be assessed from the presence of GCA activity including investigator assessment of signs and symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss [permanent vision loss due to AION, amaurosis fugax, episodic blurry vision], diplopia, or otherwise unexplained mouth or jaw pain upon mastication [i.e., jaw claudication], PMR symptoms [shoulder and/or hip girdle pain associated with inflammatory stiffness], and other features such as new or worsened extremity claudication, and fever of unknown origin), and laboratory results for serum ESR and CRP levels.

9.9. Patient's and Physician's Global Assessment of Disease Activity

The Patient's and Physician's Global Assessments of Disease Activity will be recorded on a visual analog scale (VAS). The scale for each ranges from 0 to 100 with the subject's disease activity assessment ranging from "very well" (0) to "very poor" (100). The scale for the physician's assessment ranges from "no GCA activity" (0) to "extremely active GCA" (100). The evaluating physician and subject must complete the global assessment independently of each other. The physician should preferably be the same person at every study visit for a given subject.

9.10. Pain Assessment

Subjects will be asked to assess their average pain now on a VAS ranging from "no pain" (0) to "the worst possible pain" (100).

9.11. Disease activity/damage

The Vasculitis Damage Index (VDI) will be assessed at baseline (M0) and the visit following completion of study drug (M12). The Birmingham Vasculitis Activity Score (BVAS) will be recorded at all visits including the 12-week follow up visit (M15).

9.12. Study Completion

A completed subject is one that has completed the screening period, been enrolled in the 52-week open-label enrollment period and has attended the 12-week post-treatment follow up visit. The end of the study is defined as the last subject's last visit.

10. WITHDRAWAL/STOPPING CRITERIA

10.1. Interruption of Investigational Product

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of an adverse event (AEs) or abnormal laboratory values that may have an unclear relationship to investigational product. Retest timing and frequency is at the investigator's discretion.

Investigational product must be held in the following situations and may be resumed as noted in the **TABLE 3.**

Table 3. Criteria for Temporary Interruption of Investigational Product

Hold investigational product if the following laboratory test results occur:	Investigational product may be resumed when:
WBC count <2000 cells/µL	WBC count ≥2500 cells/µL
ANC <1000 cells/µL	ANC ≥1200 cells/µL
Lymphocyte count <500 cells/µL	Lymphocyte count ≥750 cells/µL
Platelet count <75,000/µL	Platelet count ≥100,000/µL
eGFR <40 mL/min/1.73 m^2 (from serum creatinine)	eGFR ≥50 mL/min/1.73 m^2
ALT* or AST >5 x ULN	ALT and AST return to <2 x ULN, and investigational product is not considered to be the cause of enzyme elevation
Hemoglobin <8 g/dL	Hemoglobin ≥10 g/dL
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Severe infection that, in the opinion of the investigator, merits the IP being discontinued	Resolution of infection
Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; IP = investigational product; ULN = upper limit of normal; WBC = white blood cell. *ALT will be used for monitoring purposes. If abnormal then AST will be checked for further assessment of abnormalities. Alkaline phosphatase and total bilirubin will be obtained if evidence of liver disease present on ALT and/or AST to assess for need of drug interruption	

10.2. Permanent Discontinuation of Study Drug

Any subject who is permanently discontinued from investigational product for an AE or abnormal laboratory result should have the reason for investigational product discontinuation reported as the AE or abnormal laboratory value.

Patients will discontinue study drug if the following disease related clinical events occur during the study period:

- Unprovoked venous thromboembolism (deep vein thrombosis, pulmonary embolism)
- GCA relapse occurs with objective evidence of severe ischemic event (vision loss, stroke, critical limb ischemia)
- Second GCA relapse occurs during study period

Patients will discontinue study drug following temporary interruption of the study drug if either of the following occurs.

- Study drug has been held due to a study drug-related laboratory abnormality necessitating temporary interruption (Table 3) and the laboratory abnormality that led to the investigational hold has not returned to a level at which the investigational product can be resumed (Table 3) by 4 weeks (28 days) for renal function (as determined by eGFR) or 6 weeks for the remaining laboratory parameters (42 days) from the date investigational hold commenced. For example: Example 1: a patient would be withdrawn from the study if the renal function declined due to study drug (i.e. not intercurrent illness) and the eGFR decreased to 30 mL/min/1.73m2 and hold

commenced on January 1st.but the eGFR had not returned to ≥50 mL/min/1.73 m^2 by January 29th. Example 2: a patient would be withdrawn from the study if the WBC count decreased below <2000 cells/µL on January 1st and did not return to a value of >2500 cells/µL by February 11th.

- If following a study drug interruption for an identified laboratory abnormality (Table 3) the same laboratory parameter that led to study drug interruption is again affected by reinitiation of study drug. For example, platelet count prior to study drug was 150,000/uL but decreases to 50,000/uL while on the study drug. Study drug is held and the platelet count improves to 125,000/uL allowing reinitiation of study drug. Following reinitiation the platelet count decrease again to 50,000/uL.
-

In addition discontinuation of the study drug will occur if any one of the following laboratory abnormalities occur:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks after temporary interruption of investigational product
- ALT or AST >3 x ULN and either total bilirubin level (TBL) >2 x ULN or INR >1.5 x ULN
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Alkaline phosphatase (ALP) >3 x ULN
- ALP >2.5 x ULN and TBL >2 x ULN
- ALP >2.5 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Subjects should be discontinued from the investigational product in the following circumstances:

- WBC count <1000 cells/µL
- ANC <500 cells/µL
- Lymphocyte count <200 cells/µL
- Hemoglobin <6.5 g/dL

For lab values that meet permanent discontinuation thresholds, the study drug will be discontinued unless, in the opinion of the investigator, the lab abnormality is due to intercurrent illness or another identified factor. Lab tests may be repeated within 1 week to confirm whether discontinuation criteria have been met. Furthermore, if investigational product is not discontinued due to intercurrent illness, the investigator must confirm the lab value no longer meets discontinuation thresholds following the resolution of the intercurrent illness or other identified factor**.**

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

- Pregnancy
- Malignancy (except for successfully treated basal cell or squamous epithelial skin cancers)

Some possible reasons that may lead to permanent discontinuation include:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the patient should be discontinued from the study
- Subject Decision
    - the subject requests to be withdrawn from the study.

The following actions must be taken in relation to a subject that fails to attend the clinic for a required study visit.

- Site must attempt to contact the subject and re-schedule the missed visit as soon as possible
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study
- In cases deemed “lost to follow-up”, the investigator must make every effort to regain contact with the subject (up to 3 phone calls to listed number and if necessary a certified letter to last known mailing address or local equivalent methods). These contact attempts will be documented in the medical record.
- Should the subject be unreachable, only then will the subject be considered to have withdrawn from the study with a primary reason of “lost to follow-up”.

Subjects who have withdrawn prematurely from the study should attend an early withdrawal visit and undergo the 12 week post-study drug follow-up period for evaluation of safety.

Subjects withdrawn prematurely from the study can be replaced by a new study entry if the study is still openly enrolling (that is has not reached enrollment of 15 subjects).

11. STUDY ENDPOINTS

Primary endpoint:	The primary endpoint is safety. The measure by which this will be determined is the following: • Incidence of adverse events (AEs) and serious adverse events (SAEs) related to the study drug
Secondary endpoint	The secondary endpoint preliminary efficacy of baricitinib (4mg, oral, daily) in patients with relapsing GCA. The measures by which this will determined are the following:

	• Relapse-free survival at week 52 • Relapse-free survival at week 24 • Duration of glucocorticoid-free remission • Number of relapses per subject over time • Change from baseline erythrocyte sedimentation rate (ESR) to end of study • Change from baseline C-reactive protein to end of study • Glucocorticoid dose (mg) at week 52 compared to enrollment • Change in BVAS from baseline to end of study

12. STUDY MONITORING AND ADVERSE EVENT REPORTING

12.1 Study Monitoring, Auditing and Inspecting

12.1.1 Study Monitoring Plan

As a service to the sponsor-investigator and to assist with the sponsor regulatory obligation to monitor study progress, this study will be periodically monitored during the conduct of the trial by staff from the Mayo Clinic Office of Research Regulatory Support (ORRS). Clinical trial monitoring may include but will not necessarily be limited to review of the study regulatory documents, source data and database entries throughout the duration of the study to help ensure the validity and integrity of the data. Original informed consent forms will be reviewed. Written monitoring reports with findings and recommended and suggested corrective actions will be provided to the sponsor.

12.1.2 Auditing and Inspecting

The investigator will permit study-related monitoring by ORRS and audits by the IRB Compliance Unit, if indicated, as well as inspections by authorized representative of government regulatory agencies such as FDA of all study related documents (e.g. source documents, regulatory documents, data collection instruments, drug accountability records and study data etc.). The investigator will ensure access is granted for inspection of applicable study-related facilities (e.g. pharmacy, diagnostic laboratories, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

12.1.3 Ethical Considerations

This study is to be conducted according to applicable United States government regulations and Institutional research policies and procedures.

This protocol and any amendments as well as subject materials such as the informed consent/assent forms will be submitted to a properly constituted Mayo Clinic Institutional Review Board (IRB for review and formal approval. The decision(s) of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent (or assent) form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The

formal consent of a subject, using the IRB approved consent or assent form, must be obtained before subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, as well as the individual obtaining the informed consent

12.2. Safety

The Study Principal Investigator has primary oversight responsibility for the clinical trial. All co-investigators will report AEs and SAEs to the principal investigator upon alert of occurrence. Safety will be assessed from the documentation of adverse events and review of vital signs and laboratory assessments including complete blood counts, serum chemistry profiles, fasting serum lipids, and hepatitis B and C serologies. Adverse events (including serious and opportunistic infections, cardiovascular events, gastrointestinal perforations, hepatic laboratory abnormalities, and cytopenia) will be monitored on a regular and/or event-driven basis throughout the study.

The definitions of an adverse event (AE) or serious adverse event (SAE) in the following section will comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for good clinical practice and applies the standards set forth in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0.

12.3. Adverse Events

An adverse event (AE) will be defined as any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

Events meeting AE definition include:

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that do not meet AE definition include:

Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4. Serious Adverse Event

Defined according to 21CFR 312.32. A serious adverse event (SAE) is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening
- Requires hospitalization or prolongs existing hospitalization
- Is a congenital anomaly/birth defect
- An important medical event may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

12.5. Toxicity Grading of Adverse Events

Toxicity grades for AE will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). AEs will be recorded and graded 1 to 5 according to the CTCAE grade outlined below:

- Grade 1 = mild adverse event
- Grade 2 = moderate adverse event
- Grade 3 = severe and undesirable adverse event
- Grade 4 = life-threatening or disabling adverse event
- Grade 5 = death

12.6. Time Period and Frequency for Collecting Event Information

- AEs and SAEs will be collected from the start of Study Treatment until the 12 week follow-up visit and documented at time of occurrence and each study visit.

- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section and will not be considered treatment related side effects.

- Any SAEs assessed as related to study participation or related to the investigational product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

- All SAEs will be recorded and reported to the Sponsor (Mayo Clinic) and Eli Lilly [Investigational Product (IP) Manufacturer] within 24 hours.

- Investigators are not obligated to actively seek AEs or SAEs in former study subjects (those whom have completed the study including the 12 weeks post-study drug visit). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify Mayo Clinic (Sponsor) and the IP manufacturer.

12.7 Method of Detecting AEs and SAEs

Open-ended and non-leading verbal questioning of the subject will be used to inquire about AE occurrence. Such questions include:

- “How are you feeling?”

- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

12.8. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. All SAEs and their outcomes will be reported to the Food and Drug Administration (FDA).

AEs of special interest include total or partial blindness, limb claudication, and scalp or tongue necrosis. In addition, severe disease flares, including hospitalizations will be monitored.

Other AEs of special interest for baricitinib are hematologic laboratory abnormalities, hepatobiliary laboratory abnormalities and lipid parameter abnormalities. Changes in these values leading to temporary or permanent discontinuation of the study drug will be reported as an AE. Additional events of interest include serious CV events, infections and malignancies.

All initial reports of cardiovascular AEs (myocardial infarction, stroke, death, hospitalization for angina, hospitalization for TIA), newly identified malignancies and active TB will be recorded by the investigational staff within 24 hours of their knowledge of the event even if these events do not meet the definition of a SAE.

Glucocorticoid-related AEs such as diabetes mellitus, osteoporosis, fractures, infection, glaucoma, and cataracts among others will be evaluated in relation to steroid exposure and baseline risk.

12.9. Cardiovascular and Death Events

All cardiovascular events and all deaths, whether or not they are considered SAEs, will be documented. Major Adverse Cardiovascular Events (MACE), defined as myocardial infarction, stroke, death, hospitalization for unstable angina, and hospitalization for TIA, will be collected.

Definition of Cardiovascular Events:

Investigators will be required to fill out an adverse event form for the following cardiovascular events if they occur in the subject following the initiation of study drug.

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep vein thrombosis/pulmonary embolism
- Revascularization

12.10. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor and the FDA of all SAEs related to study treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met. Upon identification or knowledge of a SAE, investigators will alert the Sponsor and the IP manufacturer within 24-hours through MedWatch reporting form.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Eli Lilly policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the IP manufacturer will notify the IRB/IEC, if appropriate according to local requirements.

Expedited Adverse Event Reporting Criteria to the IP Manufacturer (Eli Lilly)

The PI or designee will report all Serious Adverse Events to the IP Manufacturer within 24 hours of the Investigator(s) becoming aware of them.

Fax all SAE forms to: Lilly Global Patient Safety at 866-644-1697

Additionally, the IP manufacturer will be provided with copies of all investigational product-related reports submitted to regulatory authorities.

12.11. Pregnancy

Given the age group under investigation, pregnancy during the course of the study is unlikely. Nevertheless, if a pregnancy is reported then the investigator will inform the IP manufacturer, Eli Lilly, within 24 hours of learning of the pregnancy.

Female subjects who become pregnant during the study must have study drug withdrawn immediately and be withdrawn from the study. An early withdrawal visit and 12-week follow-up will still occur. Information regarding the patient and fetal outcome for patients that become pregnant during the study will continue until the end of the pregnancy and result of the final outcome will be reported to the IP manufacturer for monitoring purposes.

12.12. Physical Exams

A complete physical examination will be conducted during screening and will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal, Vascular and Neurological systems. Height and weight will also be measured and recorded.

A brief physical examination will be conducted at all other time points and include, at a minimum assessments of the skin, lungs, CV system, and abdomen (liver and spleen). Investigators will pay special attention to clinical signs related to previous serious illnesses.

12.13. Vital Signs

Vital signs will be measured in seated position and will include temperature, systolic and diastolic blood pressure and pulse rate.

12.14. Clinical Safety Laboratory Assessments

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 12 weeks after the last dose of study treatment will be repeated until the values return to normal or baseline.

13. SAMPLE SIZE AND COMPUTATION RATIONALE

The study is intended to examine safety and to explore preliminary signal of efficacy. The sample size of 15 was based upon a sufficient number of subjects to begin such explorations prior to pursuit of a

randomized controlled trial. With an accrual of 15 evaluable subjects, there is a 95% confidence that any AE (or SAE) with an incidence of at least 18% will be reported. The standard error of the estimate of the incidence of reported AEs will not exceed 13%.

A historical cohort of patients with biopsy-proven GCA from the Mayo Clinic has recently been reported [16]. In this large single-institution cohort, we found the rate of second relapse in the subset of patients with at least one relapse was 50% at one year (or 50% relapse-free survival at one year). These relapses occurred during GC treatment performed at the discretion of the treating provider and patients were not subject to an accelerated taper, thus likely overestimating relapse-free survival at one year after initial relapse. A recent completed clinical trial evaluating the use of abatacept in GCA with standardized taper has been completed and preliminary results are available [42]. Relapse-free survival at one year in the placebo group was 31% and 48% in the treatment group. The relapse-free survival in Langford et al. study may also be slightly overestimated because all patients received three months of study drug prior to undergoing a standardized GC taper. Prior clinical trials in GCA have observed one year relapse-free survival among placebo groups to range from 10-29% [23,24,43]. With a sample size of 15 patients, an exact binomial test will have 80% power to detect an additional 37% above the expected relapse-free rate with a 0.05 one sided-significance level. Based on available clinical trial data and the preliminary results from Langford et al. [42] a conservative expected relapse-free survival in patients with relapsing GCA receiving only GC and undergoing an accelerated taper would be a 30% relapse-free survival at one year. As such, evidence of efficacy can be identified if 10 of 15 (67%) patients receiving study drug remain relapse-free during the study period.

14. STATISTICAL ANALYSIS PLAN

The primary purpose of this pilot study is to evaluate the safety of baricitinib in subjects with GCA. No specific statistical hypothesis tests are planned. Safety data will be summarized for all treated subjects using appropriate tabulations, descriptive statistics, and graphical presentations. The incidence rate of each AE will be estimated and reported as number (n) and percentage (%).

Descriptive statistics will be provided for all secondary outcome measures. Differences between glucocorticoid dose (mg), C-reactive protein (mg/L), erythrocyte sedimentation rate (mm/hr) and BVAS score from baseline to end of study will be calculated and reported with means and standard deviations. The proportion of subjects in sustained remission will be reported with exact 95% confidence intervals. Kaplan-Meier methods will be used to evaluate relapse-free survival and the duration of glucocorticoid-free remission. Number of relapses per subject over time will be reported as relapses/year.

15. PUBLICATION STRATEGY

This study will be registered with ClinicalTrials.gov prior to enrolling the first subject and the ClinicalTrials.gov Identifier (NCT#) will be included in manuscripts pertaining to this study. Results will be reported according to the requirements for applicable clinical trials.

Data generated from this study will be presented at national and international meetings pertaining to rheumatology (e.g. American College of Rheumatology and European League Against Rheumatism). Manuscript publication will target a high impact journal (Arthritis & Rheumatology).

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