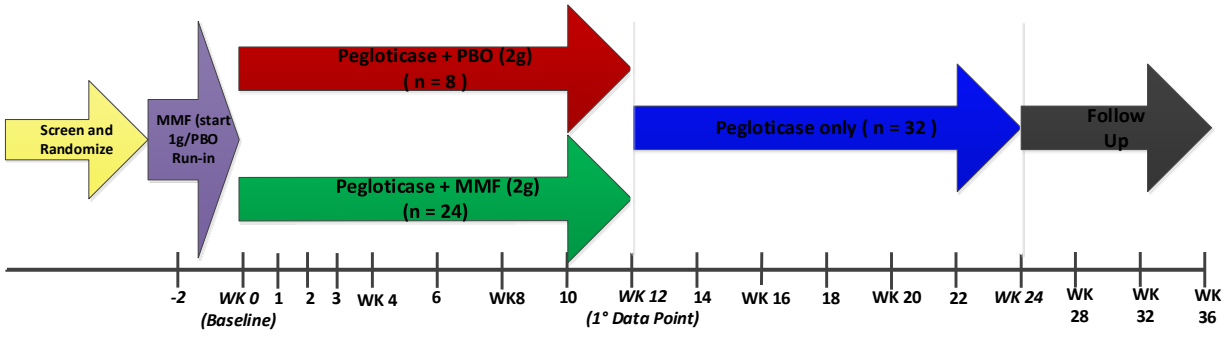
	assessing the absolute change in serum urate from baseline to Week 24, and Week 12 to Week 24, and b) determining the proportion of participants with serum urate ≤ 6 mg/dL through 24 weeks, and Week 12 to Week 24; 2) Identify and characterize the pegloticase immune response by immunoglobulin isotypes (IgG and IgM), specificities, and antibody titer, and 3) Examine patient reported outcomes (PROs) using the National institute of Health (NIH) supported Patient Reported Outcomes Measurement Information System (PROMIS) and Gout Impact Scale (GIS) instruments.
Study Population:	We will enroll 32 adults (≥ 18 years of age) diagnosed with chronic refractory gout, defined as persons whose signs and symptoms are inadequately controlled with urate lowering therapy (e.g. xanthine oxidase inhibitors or uricosuric agents) at a medically appropriate dose or for whom these drugs are contraindicated. Recruitment will include men and women of all races/ethnicities.
Phase:	Phase II Trial
Description of Sites/Facilities Enrolling Participants:	University of Alabama at Birmingham (Study Clinical Coordinating Center and Data Coordinating Center); University of Michigan.
Description of Study Intervention:	Phase II, double blind, placebo controlled multisite proof-of-concept trial in participants initiating pegloticase for treatment of chronic refractory gout**.** Participants will be randomized (3:1) to one of two study arms, a pegloticase + MMF or a pegloticase + placebo study arm study arm. **Experimental**: pegloticase + MMF Participants randomized to this arm will receive pegloticase + MMF **Placebo Comparator**: pegloticase + placebo (PBO) Participants randomized to this arm will receive pegloticase + placebo
Study Duration:	24 months
Participant Duration:	Up to six months (24 weeks)

2.2 SCHEMA

Figure 1. RECIPE Study Patient Level Timeline



3 INTRODUCTION

3.1 STUDY RATIONALE

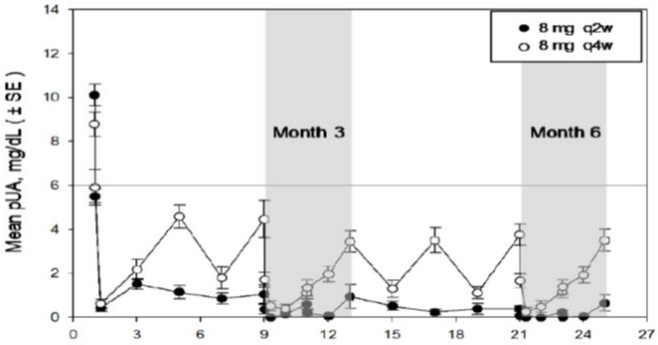
Pegloticase, a recombinant modified mammalian urate oxidase (uricase), that is approved by the Food and Drug Administration (FDA) and the European Commission for use in gout patients is very efficacious in reducing serum urate (**Figure 2**) and improving clinical signs and symptoms of gout, such as tophi size (**Figure 3**).[1-5] However, pegloticase has been associated with a high rate of infusion reactions (IRs) including anaphylaxis.

The ability of pegloticase to induce antibody production (leading to the need to stop therapy) raised the possibility that by reducing anti-pegloticase antibodies via an immune modifying drug, the loss of response to the drug could be prevented or delayed, as proposed in this study.[6]

3.2 BACKGROUND

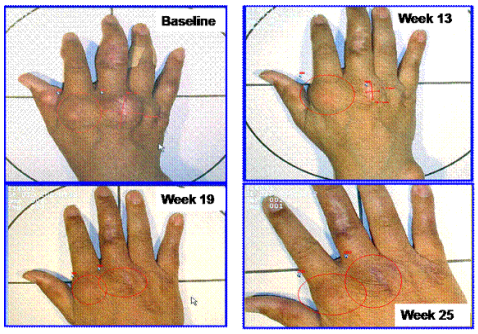
Gout affects approximately 4% of the U.S. population, is the most common form of inflammatory arthritis in men, and is associated with decreased quality of life.[7-9] The frequency of gout is increasing worldwide, with prevalence rates estimated to be as high as 7% in older men, based on our work and the work of others.[10-12] It is estimated that up to 400,000 (up to 5% of the estimated 8 million persons with gout) in the United States experience chronic refractory gout, characterized by ongoing symptoms of active disease and a failure to control/maintain serum urate < 6 mg/dL with conventional xanthine oxidase inhibitors (i.e. allopurinol and febuxostat) and uricosuric agents (i.e. probenecid).[2,13-15] These patients often have significant, disabling urate deposits in soft tissues and bone known as tophi.

Figure 2. Urate reducing efficacy of pegloticase [1]



As stated in the study rationale (section 2.1), pegloticase has been associated with a high rate of infusion reactions (IRs) including anaphylaxis. IRs occurred in 26% of participants on pegloticase compared to 5% in placebo, and anaphylaxis was reported in 5% of participants on pegloticase vs. 0% on placebo.[5] Additionally, in one study the drug's immunogenicity leads to anti-pegloticase antibody (Ab) formation and associated loss of efficacy manifested by a rapid increase in serum urate levels in roughly 42% of all participants (n=212).[5,16]

Figure 3. Hand tophi and sequential response to pegloticase [2,3]



A relationship between the loss of urate-lowering efficacy (indicated by a rise in serum urate levels) and high-titer antibody formation was initially identified in a post-hoc analysis of two studies.[1,5] Participants with high anti-pegloticase antibody titers (>1:2430) experienced a significant loss of pegloticase activity that was attributed to more rapid clearance of drug in the presence of these antibodies. Sixty-nine (41%) of 169 patients receiving pegloticase developed high titer anti-pegloticase antibodies and subsequently lost response to the drug.[17] In a second study, only 1 of 52 participants with high antibody titers maintained a response to pegloticase (serum urate < 6.0 mg/dL).[5] In addition, 60% participants with high titers developed IR.[5,18] Anti-pegloticase antibodies were largely directed to the polyethylene glycol (PEG) portion of the molecule and altered the pharmacokinetic clearance of pegloticase, resulting in inhibition of serum urate lowering activity.[17]

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		responders will produce both IgM and IgG antibodies at earlier onset
To assess patient reported outcomes (PRO)	PROs using PROMIS and Gout Impact score	To assess impact of the intervention on patient reported outcomes
Tertiary/Exploratory		
Not applicable		

5 STUDY DESIGN

5.1 OVERALL DESIGN

Hypothesis: MMF for 12 weeks can safely attenuate immunogenicity conferred by pegloticase as determined by the proportion of participants achieving and maintaining an sUA ≤ to 6 mg/dL through 12 weeks, compared to concurrent controls
Phase of trial: Phase II
Design of trial: Randomized, double-blind, placebo controlled
Single or multi-site: Multisite (UAB, University of Michigan[UM], and up to 6 to be named sites)
Number of Arms: Two arms; Intervention Arm: pegloticase + MMF (peg + MMF); Placebo Comparator Arm: pegloticase + placebo (peg + PBO)
Methods to minimize bias: Participants will be randomized 3:1 to either peg+MMF or to peg+PBO. Randomization allocation will be balanced by site to achieve 24 peg+MMF and 8 peg+PBO using the double-blind design

During the first 12 weeks, participants randomized to the peg+MMF arm will receive a combination of pegloticase and MMF. Patients experience reduced immunogenicity when a loading dose of anti-proliferative agent is administered *prior* to a monoclonal antibody in other disease states,[27-30] thus, for those randomized to the peg+MMF arm we will begin a MMF run-in at 500 mg/twice per day for the first week, and if tolerated titrate the dose up to 1000mg/twice per day for the second week of run-in prior to initial pegloticase infusion. MMF (or matching PBO in the other arm) will be titrated to 1000 mg/twice per day (a standard, well-tolerated dose used in other rheumatic diseases)[6] concurrent with the first pegloticase infusion. Next, a total of up to 12 infusions of pegloticase 8 mg IV will be administered on a biweekly basis. To understand the long-term efficacy (durability) and safety of this approach, and to minimize the exposure to MMF, following the first 12 weeks of dual therapy phase, all participants will be given an additional three months of open-label pegloticase only therapy (see **Figure 1**) and will be followed.

5.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study is designed as a standard superiority double-blind, randomized controlled clinical trial. This study design has the highest validity to address the question posed.

5.2.1 RATIONALE FOR A PEGLOTICASE IMMUNOGENICITY TRIAL

Immunogenicity in response to pegloticase therapy (anti-pegloticase antibodies) may give rise to low serum drug levels, loss of therapeutic response, poor drug survival and/or adverse events (e.g., IR). The development of anti-drug antibodies can be influenced by drug- and treatment- related factors, as well as participant characteristics.[16] A potential prophylactic strategy to manage anti-drug antibody response with biologic response modifiers is the co-administration of immune modulating therapy.[16,31-35] Reduction of immunogenicity with concomitant administration of other biologic agents (e.g. methotrexate use with adalimumab, infliximab) has been attributed to two mechanisms: 1) an immune

modulating effect downregulating B cell activation, differentiation, and immunoglobulin production, and 2) alteration in Fc gamma R-mediated clearance mechanisms leading to prolongation of the half-life of monoclonal antibodies.[31,36,37] How these mechanisms extend to pegloticase is unknown and will be addressed in this study.

In a randomized controlled trial (RCT) for lupus nephritis patients were treated concomitantly with mycophenolate mofetil (MMF) and glucocorticoids, and randomized to receive either rituximab or placebo. Over the 78 week study period the serious adverse event rate, including infections, were similar in both groups and did not result in differential or unexpected safety signals. The rate of serious infections (19.9/100 patient-years and 16.6/100 patient-years in the placebo and rituximab arms, respectively) in this combination immunotherapy study is relevant for our proposed investigation since gout flares may be treated with glucocorticoids, which may also increase infection risk.[38] In an open-label trial, thirty participants received pegloticase every three weeks for five infusions to investigate Ab response.[6] Seven of these participants (3 of whom were on MMF receiving doses ranging from 500 – 2000 mg per day) were organ transplant recipients.[5,6,21] Only one out of seven organ transplant recipients had a sustained high titer Ab response to pegloticase. Thus, organ transplant recipients on immune modulating therapies may be less prone to developing anti-pegloticase Ab, but further investigation of safer, shorter-term immune modulating strategies to minimize anti-pegloticase Ab are needed, as we propose with MMF.

The above cited data provide the background rational for our hypothesis that the addition of immune modulating therapy with an induction regimen or loading dose provides additive benefit in abrogating immunogenicity associated with biologics. For this study, we have selected the immune modulating agent, mycophenolate mofetil (MMF) for use as a short course therapy to improve treatment efficacy and reduce IR in patients being treated for chronic gout with pegloticase.

5.2.2 RATIONALE FOR MYCOPHENOLATE MOFETIL (MMF) AS THE PREFERRED IMMUNE MODULATING AGENT

In this proof-of-concept study, we will test the principle that a short-term course of MMF can mitigate immunogenicity to pegloticase and we will evaluate the ability of MMF to suppress formation of anti-pegloticase antibodies. The rationale for exploring this question with MMF as the immune modifying drug was based on several factors: 1) common and successful use of MMF as an immune modulating drug in other diseases; [30,39-41] 2) favorable risk/benefit ratio for MMF in the potential study population (see paragraph below); and 3) a survey of rheumatologists. We believe MMF is an excellent choice to modulate immunogenicity to pegloticase due to its ability to target the mechanism of pegloticase immunogenicity through inhibition of T and B cell proliferation.[42,43] MMF, the pro-drug of active moiety mycophenolic acid, is a potent, selective, and reversible inhibitor of inosine monophosphate dehydrogenase, the key enzyme of *de novo* purine synthesis in activated lymphocytes. The main adverse effects associated with oral MMF are gastrointestinal and hematologic (leukopenia) and are relatively mild in most participants.[40] MMF is used extensively in the management of systemic lupus erythematous and other immune mediated illnesses.[30,39-41,43,44]

We considered but rejected other possible immune modulators in combination with pegloticase. In contrast to MMF, azathioprine (AZA) metabolism is affected by allopurinol; a significant disadvantage for participants with gout even those in a clinical trial (that excludes allopurinol) would be at risk of inadvertently receiving this therapy from non-study physicians.[45-47] Moreover, AZA metabolism is dependent on the thiopurine methyltransferase pathway and we would need to measure this enzyme activity, it is less well tolerated than MMF, and requires extended titration.[48,49] Also in contrast to MMF, methotrexate (MTX) requires a longer run-in time and gradual dose titration to induce clinically meaningful suppression of T and B cells. MTX is likely to be problematic in patients with severe gout and multiple comorbidities (e.g. chronic kidney disease), who may be at higher risk for alcohol use, and who demonstrate more frequent steatohepatitis, thus placing them at higher risk for side effects (e.g., folate deficiency anemia and liver dysfunction).[50,51] With MTX, and also with leflunomide, we were concerned about potential impact on liver/kidney toxicity and the possible confounding benefit of lowering serum urate and suppressing gouty attacks, effects previously reported with both agents.[51-53]

Adherence to the medication will be recorded by pill counts at the follow-up study visits and consumption of at least 80% will be required to consider the participant compliant. A non-compliant participant will continue in the study and enter analyses as mandated by statistician. Pill counts and infusion log will be used to calculate study intervention compliance. Other issues of non-adherence to study procedures will be reinforced with participants at study visits and recurrent non-adherence will lead to study discontinuation.

7.5 CONCOMITANT THERAPY

Concomitant medications are defined as drug or biological products other than the study drug(s) taken by a participant during the clinical trial. This includes other prescription medications (including preventive vaccines), over-the-counter medications, herbal medications, vitamins, and food supplements. A comprehensive list of participant's concomitant medications will be collected at baseline and at V2, V3, V5, V7-V17 each visit. This will include the name of the drug/vitamin/supplement, dose, route of administration, start and stop dates, and the reason for which the medication was taken. All medications will be listed by participant using the generic name(s) of the drug/vitamin/supplement. Serious adverse events related to the use of a concomitant drug/vitamin/supplement will be documented on the appropriate AE eCRF.

Prior to participation in RECIPE participants will be instructed to stop their current urate lowering therapy.

7.5.1 RESCUE MEDICINE

There is no specific rescue medication for mycophenolate adverse events. Overdose of MMF will be managed with prompt decontamination via activated charcoal, symptomatic management of nausea and vomiting along with adequate hydration.[54] Adverse effects associated with MMF are subsequently reviewed in section 8.3.3.3.

All participants will receive prophylactic treatment to reduce the risk of acute gout flares, unless medically contraindicated or not tolerated as noted in the FDA-approved pegloticase full prescribing information. The participant will begin a regime of colchicine (0.6mg/day) or Non steroidal anti-inflammatory drug prophylaxis at least 1 week before the first dose of pegloticase and it will continue for the duration of pegloticase therapy. Colchicine prophylaxis will not be interrupted during the course of the clinical trial unless medically contraindicated or if the participant becomes intolerant of colchicine, regardless of whether a gout flare occurs.

At the discretion of the investigator, patients still having insufficient relief with colchicine (0.6mg/day) or Non steroidal anti-inflammatory drug prophylaxis are allowed to take oral prednisone, prednisolone or equivalent at a dose up to 20 mg/day for a maximum of 7 days.

8 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 DISCONTINUATION OF STUDY INTERVENTION

Due to the risk of anaphylaxis and IRs being higher in patients who have lost therapeutic response, participants with two consecutive serum urate levels above 6 mg/dL shall be classified as a non-responder and discontinued from the study. Investigators will obtain a pre-dose serum urate sample for all patients and review results to verify the serum urate level is ≤ 6 mg/dL prior to infusion.

Discontinuation from the study intervention does not mean discontinuation from the study, and remaining study

- Respiratory
- Gastrointestinal
- Musculoskeletal
- Neurologic
- Integumentary
- VS/Measurements

- Gout Flare/ assessment
- PROs (eg. PROMIS-29 & GIS instrument)
- Blood draw
- Screening Visit Laboratory
  - CBC with diff
  - HIV1 and 2 Antibody Screen
  - IgG
  - sUA
  - Pregnancy test for premenopausal women
  - Comprehensive Metabolic Panel (CMP)
  - G6PD
  - Specimen collection (blood sample for serum banking)
  - Pegloticase Antibody/Mechanistic Study

Vital signs will consist of heart rate, respiratory rate, blood pressure (noting the position in which it was obtained), and body temperature (taken either orally or aurally). All measurements of pulse rate and blood pressure should be made after approximately 5 minutes of rest. Focused history and physical examination: Information collected will include date of birth, self-reported race/ethnicity (defined as in previous studies investigating its role in rheumatic diseases,[1] gout history, medication history (including use of aspirin, gout medications), weight, and height. Assessments for presence of tophi will be conducted as well as gout history and symptom severity.

- Document the number of gout flares in the last 6 months and 12 months and the most recent occurrence. Patients with gout flares can enter the study if the flare treatment is discontinued 1 week prior to the first dose of pegloticase.
- Document the presence and/or history of gout-related kidney disease.

Physical examinations will be performed by body system at Screening, Visit 11, and Visit 17 (end of treatment) or early termination visit in the pegloticase dosing phase. Significant findings prior to the administration of pegloticase must be recorded in the patient's medical record and included on the Medical History in the eCRFs. Significant findings that occur after administration of pegloticase which meet the definition of an AE must be recorded in the medical record and on the Adverse Events eCRF page.

All women of childbearing potential must use an effective form of birth control during this study and for 30 days after completion of the study. Acceptable methods of birth control include hormonal control methods, inter-uterine device, a double-barrier method (diaphragm with spermicide, condom with spermicide) or abstinence. All male participants will be cautioned to use proper birth control methods with their partners during the course of the study in which MMF is received.[3]

Laboratory: sUA, CMP, CBC with diff, and pregnancy test for premenopausal women. Additionally, a sample will be collected at screening, Visits 1, 8, 11, 14, and 17-20 for evaluation of anti-pegloticase Ab. Serum samples (see **Appendix 5)** will be collected and prepared for transport to the clinical research lab in the Division of Clinical Immunology and

Vital signs: consisting of heart rate, respiratory rate, blood pressure (noting the position in which it was obtained), and body temperature will be performed at Visit 1, 2, 3, 5, 7-17.

Biological specimen collection: Following Screening Visit, Visits 3, 8, 11, 14, 17-20, and any unscheduled visits a biospecimen will be collected for measurement of antibody response. Additionally, in the event a participant experiences an infusion reaction during a specimen will be collected, as high titer anti-pegloticase antibodies have been associated with a loss of responsiveness to pegloticase and increased infusion reactions.

Assessment of study intervention adherence: Infusion logs and pill counts (during the first 12 weeks) will be kept measure participant adherence to the study intervention.

Assessment of adverse events: Significant findings that occur after administration of pegloticase which meet the definition of an AE will be recorded in the medical record and on the Adverse Events care report forms.

9.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

This is a Phase II, double-blind, placebo controlled examining two medications (pegloticase and MMF) that are already FDA approved and have been in clinical use for over 5 years, but are not commonly co-administered. Any worsening (i.e. any clinically significant adverse change in frequency or intensity) of a preexisting condition which is temporally associated with the use of pegloticase or MMF is also considered an AE. Abnormal laboratory values or test results will constitute AEs if they differ significantly from baseline, and will be recorded in the CRF. Screening conditions will not be considered AE; however, worsening of a preexisting condition may be considered an AE. We will start collecting AEs at Visit 3. All AE and SAE's will be able to be reviewed electronically via the eDES and electronic medical record.

The safety events of interest in assessing study risks and benefits are IRs and a co-primary study outcome. Participants will be followed for the occurrence of IR and secondary outcomes of interest events at each study visit. Supplementing the data collected during these visits will be information collected regarding participant reported health-related quality of life (QOL), and for improved, near real-time assessment of outcome events. Non-serious events that are expected according to previous experience with the study drugs (pegloticase, MMF) as described in the protocol, consent materials, or any approved product labelling will also be collected. We will report all serious AEs according to appropriate authority (e.g., NIAMS, FDA, IRB) in compliance with guidelines and regulations.

9.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A SAE is any AE occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (places the participant, in the view of the site PI, at immediate risk of death from the AE as it occurred)
- Inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if hospitalized as a precautionary measure for continued observation)
- A permanent, persistent, or significant disability (substantial disruption of the ability to conduct normal life

functions). A medically significant AE that may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Events NOT considered to be **Serious** are:

- Hospitalization for treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- Treatment on an emergency, outpatient basis for an event NOT fulfilling any of the definitions of serious given above and NOT resulting in hospital admission
- An event that, had it occurred in a more serious form, might have caused death
- A sign, symptom, or event that is noticeable but easily tolerated.
- An event does not significantly influence performance or prevent the participant from carrying on with their usuall life activities.

9.3.3 CLASSIFICATION OF AN ADVERSE EVENT

9.3.3.1 SEVERITY OF EVENT

The severity of adverse changes in physical signs or symptoms will be classified as follows:

- Grade 1 (Mild): Asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.
- Grade 2 (Moderate): Minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL (Activities of Daily Living).
- Grade 3 (Serious): Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 (Life-threatening): Consequences; urgent intervention indicated.
- Grade 5 (Death): Event is a direct cause of death.

A sign, symptom, or event that causes serious discomfort to the participant and significantly affects clinical status or the ability to perform normal daily life activities. Treatment intervention is warranted.

9.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

An event is related to the research if, in the opinion of the UAB/UM investigator, it was more likely than not to be the result of the interventions and interactions used in the research (i.e., there is a reasonable possibility that the event may have been caused by participation in the research).

The determination of the likelihood that the study drug caused the AE will be provided by the site PI. The site PI's signature and date on the source document and eCRF that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. The assessment of relationship will be reported by the site PIs according to his/her best clinical judgment the following scale of criteria may be used as a guidance (not all criteria will be present in order to be indicative of a drug relationship).

Definitely Related to the Research:

- There is evidence of exposure to the study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- The AE is explained by the study drug

Probably Related to the Research:

- There is evidence of exposure to the study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- The AE is more likely explained by the study drug than by another cause

Possibly Related to the Research:

- There is evidence of exposure to study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- The AE could have been due to another equally likely cause

Unlikely Related to the Research:

- There is evidence of exposure to the study drug
- There is another more likely cause of the AE
- There is no temporal relationship to study drug

Unrelated to the Study Drug:

- There is no evidence of exposure to the study drug
- There is another more likely cause of the AE
- There is no temporal relationship to study drug

For all presumed Serious/SAE a study safety event report will completed and submitted to the Data Safety Monitoring Board (DSMB) (see MOOP Section 2.m) and IRB after validation of event. Monitoring of these outcome events will begin as soon as a study participant is enrolled and will continue until the end of the observation period. The DSMB will provide independent oversight and act in an advisory capacity to monitor research participant safety and data quality and to alert the NIAMS to potential issues.

9.3.3.3 EXPECTEDNESS

Expected potential AEs Associated with MMF (see also section 2.3.1)

- Gastrointestinal: Nausea and vomiting (12%), diarrhea
- Hematologic & oncologic: Leukopenia (renal transplant: > 50%; RA: 28%), neoplasia (renal transplant: 3% (other than lymphoma), 0.5% (lymphoma)), thrombocytopenia
- Hepatic: Hepatotoxicity, increased serum alkaline phosphatase, increased serum bilirubin, increased serum transaminases
- Infection: Increased susceptibility to infection (renal transplant 20%; RA <1%; includes bacterial, fungal, protozoal, viral, opportunistic, and reactivation of latent infections)

Expected potential AEs associated with Pegloticase (see also section 2.3.1)

During pre-marketing controlled clinical trials, infusion reactions were reported in 26% of patients treated with pegloticase 8 mg every 2 weeks. During pre-marketing controlled clinical trials, anaphylaxis was reported with a frequency of 6.5% for patients treated with pegloticase. For the purposes of this study, these events shall be defined as follows:

- IR (see Section 8.3.8.1) not attributable to another cause that occurs during or within 2 hours after the

severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 (for SAEs) days after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

9.3.5 ADVERSE EVENT REPORTING

We will report all serious AEs according to appropriate authority (e.g. IRB, NIAMS, FDA) in compliance with guidelines and regulations established by the Data Safety Monitoring Board. See **Appendix 9** Data Safety Monitoring Plan.

9.3.6 SERIOUS ADVERSE EVENT REPORTING

We will immediately report to the DSMB and any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and will include an assessment of whether in the view of the site PI there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) will be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator will report the event to the NIAMS and DSMB via KAI within 48 hours of the investigator becoming aware of the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. All SAEs , regardless of relatedness will be reported to the NIAMS and the DSMB via KAI within 48 hours of becoming aware of the event. Supporting documentation of the event will be provided by the DCC.

The Data Coordinating Center will be responsible for notifying the Institutional Review Board, Food and Drug Administration (FDA), NIAMS/KAI, and any other body as mandated by the DSMB of any unexpected fatal or life-threatening suspected adverse reaction within 24 hours. In addition, the Data Coordinating Center will notify FDA and all participating investigators of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 15 calendar days after it is determined that the information qualifies for reporting.

9.3.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be informed about new AEs and SAEs, and on conclusion of the study, study-related results at an aggregate level.

9.3.8 EVENTS OF SPECIAL INTEREST

9.3.8.1 INFUSION REACTIONS (IRS)

As described in section 8.3.3.3 during pre-marketing controlled clinical trials, infusion reactions (IR) were reported in 26% of patients treated with pegloticase 8 mg every 2 weeks. IRs will be defined as any infusion-related AE or cluster of temporally-related AEs, not attributable to another cause, which occur during or within 2 hours after the infusion of

pegloticase. Other AEs that occur outside of the 2-hour window following the infusion may also be categorized as an IR per site PI discretion. Signs and symptoms of the IR, and treatments administered, will be documented in the medical record and in the eCRF. Examples of AEs not considered possible IRs include but are not limited to: laboratory abnormalities that are unlikely to have occurred during or within 2 hours following the infusion (e.g., anemia, hypercholesterolemia), gout flares, most infectious diseases, or the recurrence or worsening of a known chronic medical problem identified in the participant's medical history.

IRs are not uncommon when biological agents are administered by IV infusion. Therefore, all participants will receive pre-treatment prophylaxis consisting of at least an antihistamine and corticosteroid prior to each infusion of pegloticase (see **Table 2**). In order to standardize this regimen, participants will take fexofenadine (60 mg, PO) the night before and again on the morning of the infusion with acetaminophen (1000 mg, PO) Prior to the infusion, hydrocortisone (200 mg, IV) will be administered and a at minimum, a targeted physical exam will be performed. The name, dose, route, date, and time of administration of each prophylactic medication will be recorded in the medical record and in the CRF.

Table 2. Infusion Reaction Prophylaxis

Night Before Infusion	Morning of Infusion	Following Arrival at Infusion Clinic
Participant takes: Fexofenadine (60 mg) PO	Participant takes: Fexofenadine (60 mg) PO Acetaminophen (1000 mg) PO	Abbreviated physical examination to include: Dermatological – Noting Any Rashes Chest – Noting Breath Sounds Vital Signs Start IV and Administer hydrocortisone (200 mg) Initiate Drug Infusion

9.3.8.2 PREGNANCY

Premenopausal women will have a pregnancy test before the study starts and again throughout the study. If participants suspect that they may have become pregnant during the study, the study coordinator will contact the study PI immediately and the PI or Study Coordinator will instruct the participant to stop taking all study medication. If it is confirmed that the participant is pregnant, they will be withdrawn from the study. The study PI will schedule a follow-up visit and may choose to follow the outcome of the pregnancy. If it is discovered that participants are breastfeeding, they are not eligible to participate in the study and their participation will be discontinued immediately.

9.4 UNANTICIPATED PROBLEMS

9.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems, in general, are defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

effect or pattern of response with anti-pegloticase Ab titers/types. This aim will be supported by analyses that compares the treatment groups using two group t-tests and regression analyses that include the time of the sampling (an offset) to adjust for any 12 or 24 week samples that may be taken earlier at the time of failure or dropout. Repeated measures assessments using all Ab data (both data points: baseline and last observation) will be assessed using random effects in PROC MIXED to assess the variability in response over time. Comparisons will be assessed using pre-specified contrasts. Analyses of the sUA will be similarly assessed using PROC MIXED with random effects for participant. In addition, addressing the secondary aim: b) determining the proportion of participants with sUA ≤ 6 mg/dL through 24 weeks, and Week 12 to Week 24; will be examined using Fisher's exact test. Continuous models estimating the areas under the dose-time curve with estimation based on using the trapezoidal rule will be constructed and adjusted for time under study yielding an average sUA during the observation period. These areas under the curve will be compared using similar linear models with an offset for the time under study. Exploratory analyses will assess association of covariates within group areas under the curve; 2) Identify and characterize the pegloticase immune response by immunoglobulin isotypes (IgG and IgM), specificities, and Ab titer.

These secondary outcome variables will be summarized using means with standard deviation, confidence intervals, and/or median and interquartile ranges, dependent on their distribution and plots of their response alone and in combination. Secondary endpoints will examine different definitions of sUA levels by plotting the initial values versus change values on the unbiased outcome results and time weighted averages; and 3) Examine PROs using the NIH supported Patient Reported Outcomes Measurement Information System (PROMIS)[57,58] and Gout Impact Scale (GIS)[59,60] instruments; these will use similar approaches of descriptive statistics, plots of PROs versus outcomes and correlations. The PROs will be summarized by change over time using means, 95% confidence intervals and compared between responder and non-responder status. We do not plan to control for the repeated testing using adjustments for multiple comparisons since this is a feasibility trial and since statistical significance is not the goal as it would be in a pivotal trial. The sample size is small and we see these secondary as well as primary analyses as descriptive. The p-values will be calculated, but will take the totality of the evidence into account in the interpretation. We considered using hierarchical testing such that each test would be done at the 0.05 level, but the low power argues that such could easily lead back to not considering secondary endpoints.

10.4.4 BASELINE DESCRIPTIVE STATISTICS

Intervention groups will be compared on baseline characteristics and will include the following.

- Inclusion and Exclusion Criteria
- Demographics and Baseline Characteristics
- Medical History
- Disease History
- Medication History
- Laboratory values

Demographics will be summarized using descriptive statistics, by treatment group and site.

10.4.5 INTERIM ANALYSES

Not applicable for a pilot study of this nature. Safety findings that may prompt temporary suspension of enrollment and safety review are discussed in section 8.1.

10.4.6 SUB-GROUP ANALYSES

Not applicable for a pilot study of this nature

10.4.7 MISSING DATA AND OUTLIERS

We will perform imputation for the anticipated small number of missing outcomes, but as is now becoming commonly known, we expect the impact of such imputation to be minor. The imputation may be slightly different for different outcomes. For a given outcome, missing data from a visit missed that is flanked by available visits may allow for

CBC	Complete Blood Count
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulation
CMP	Comprehensive Metabolic Panel
DCC	Data Coordination Center
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
eDES	Electronic Data Entry System
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration
G6PD	Glucose-6-Phosphate Dehydrogenase
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GIS	Gout Impact Scale
GOL	Golimumab
HEENT	Head, ears, eyes, nose, and throat exam
HIV	Human Immunodeficiency Virus
IBD	Inflammatory Bowel Disease
IC	Informed Consent
ICF	Informed Consent Form
Ig	Immunoglobulin
IMPDH	Inosine Monophosphate Dehydrogenase
IND	Investigational New Drug
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IR	Infusion Reaction
IRB	Institutional Review Board
IV	Intravenous
mAbs	Monoclonal Antibodies
MMF	Mycophenolate Mofetil
MOOP	Manual of Operating Procedures
MPA	Moiety Mycophenolic Acid
MTX	Methotrexate
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH	National Institute of Health
PBO	Placebo
PEG	Polyethylene glycol
PI	Principal Investigator
PO	Per Orum
PRO	Patient Reported Outcome
PROMIS-29	Patient Reported Outcomes Measurement Information System
QOL	Quality of Life
RA	Rheumatoid Arthritis
RBC	Red Blood Cells
SAE	Serious Adverse Events
SAS	Statistical Analysis System
SOPs	Standard Operating Procedures
sUA	Serum urate
TB	Tuberculosis

2.3 TABLE 1. SCHEDULE OF ACTIVITIES (SOA)

	Screen/Run-In		Phase 1									Phase 2						Phase 3		
Study procedures	V1 (-4 wks)	V2 (-2 wks)	V3 (0 wks)	V4 (1 wks)	V5 (2wks)	V6 (3 wks)	V7 (4 wks)	V8 (6wks)	V9 (8 wks)	V10 (10 wks)	V11 (12 wks)	V12 (14wks)	V13 (16 wks)	V14 (18wks)	V15 (20 wks)	V16 (22 wks)	V17 (24 wks)	V18 (28 wks)	V19 (32 wks)	V20 (EOS/ET) (36 wks)
ICF	X																			
Medical history	X																			
Physical exam	X										X						X			
Vital signs*	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X			
PROS	X		X				X		X		X		X		X		X			
Assess flares, Update med conditions and meds		X	X		X		X	X	X	X	X	X	X	X	X	X	X			
Assess AEs[¢]			X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense MMF/PBO		X (500 mg/ 2x per day)- week 1 and X (1 g/ 2x per day)	X[¥] (1 g/2x per day)		X (1 g/ 2x per day)		X (1 g/ 2x per day)	X (1 g/ 2x per day)	X (1g/2x per day)	X (1 g/ 2x per day)										
Pill count			X		X		X	X	X	X	X									
Targeted PE/joint assess			X		X		X	X	X	X		X	X	X	X	X				
CBC with diff	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
HIV1 and 2 Antibody Screen	X																			
IgG	X		X					X			X									
sUA (Pre Infusion Weeks 0-24[++])	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X			
Pregnancy testing	X (serum)	X	X		X		X	X	X	X	X	X	X	X	X	X	X			
CMP	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X			
G6PD	X																			
Peg Ab/Mechanistic collection/ storage [£]	X		X					X			X			X			X	X	X	X
MMF Adherence			X	X	X	X	X	X	X	X	X									
Gout flare prophylaxis[‡]		X	X		X		X	X	X	X	X	X	X	X	X	X				
Administer pegloticase≠			X		X		X	X	X	X	X	X	X	X	X	X				

Ab=antibody; CBC with diff = Complete Blood Count with Differentiation; CMP = Comprehensive metabolic profile(hematology will include hemoglobin concentration and hematocrit; erythrocyte, platelet, and leukocyte counts; differential leukocyte count, serum chemistry will include transaminases, alkaline phosphatase, total bilirubin, lactic dehydrogenase (LDH), uric acid, glucose, total cholesterol, sodium, potassium, calcium, chloride, total protein, and blood urea nitrogen (BUN)); EOS= End of study; EOT= End of Term; G6PD = glucose-6-phosphate dehydrogenase (All participants will be tested for G6PD); IR = infusion reaction, HIV= humane immunodeficiency virus; MMF = mycophenolate mofetil; PROs = patient reported outcomes; The 1st dose of pegloticase will be scheduled once it has been confirmed that the participant has been on gout flare prophylaxis for at least a week and is able to take the prophylaxis IR drugs prior to the first visit. Follow-up pegloticase doses will be scheduled within 14 ± 2-days post prior dose; * Includes sitting blood pressure, heart rate, respiratory rate, and body temperature. Vital signs should be collected before study, drug infusion or pre-medications, and every 30 mins during the infusion of study drug. ¢ Includes assessment for IR (infusion reactions) when pegloticase is administered ++ The serum urate results will be used in determining if participant receives pegloticase infusion; ¥500 mg/2x per day will be dispensed at run-in per randomization assignment. Depending on tolerability will be increased to 1 gm/2x per day. £Serum samples will be collected for analysis of anti-pegloticase Ab at time points indicated above, and in the event of hypersensitivity reaction; ‡ Participants will begin a regime of colchicine or NSAID gout flare prophylaxis at least 1 week before the first dose of pegloticase and will continue for the duration of pegloticase therapy. ≠IR prophylaxis will be administered the night before ((60 mg PO) fexofenadine) and the morning of the day of pegloticase dosing ((60 mg PO) fexofenadine plus (1000 mg PO) acetaminophen); and hydrocortisone (200 mg IV) immediately prior to the infusion).

The ability of pegloticase to induce Ab production (leading to the need to stop therapy) raised the possibility that by reducing anti-pegloticase antibodies via an immune modifying drug the loss of response to the drug could be prevented or delayed, as proposed in this study.[6] The rationale for use of mycophenolate moefitil as an immunomodulatory agent to attenuate pegloticase immunogenicity is discussed in section 4.2.2.

3.3 RISK/BENEFIT ASSESSMENT

3.3.1 KNOWN POTENTIAL RISKS

The known risks for participants as a result of participation in the RECIPE study are summarized below. This includes risks associated with the proposed study medications as well physical, psychological, social, economic, and/or legal risks from participating in this study.

1. Participants may experience pain from the needle used during phlebotomy, as well as possible bruising and soreness at the phlebotomy site. Pain following injection and bruising will subside over time.

2. Participants may experience some anxiety in completing questionnaires about their gout. The questionnaires should take <20 minutes to complete. Anxiety following completion of the questionnaires should subside over time.

3. Immediate and longer-term drug specific risks for all study drugs
   All study drugs to be tested/administered in the RECIPE study are FDA approved for use in various conditions. Risk associated with each are listed below and taken from package inserts and published literature (see Appendices 4, 5, and 6):

   a. Mycophenolate Mofetil (MMF) (Oral ingestion).

   i. <u>Immediate Risks</u>
   - Nausea—20%; often subsides over time and following discontinuation of MMF
   - Persistent diarrhea—36%; Subsides over time and following discontinuation of MMF
   - Gastrointestinal bleeding requiring hospitalization—1.7%-5.4%
   - Neutropenia—2-3.6%; Subsides over time following discontinuation of MMF
   - Decreased immune function and corresponding increased susceptibility to bacterial, viral, fungal, and protozoal infections, including opportunistic infections—1%-10%
   - Other symptoms, occurring at rates of 1% to 10%, include hypertension, hypotension, tachycardia, chills, pain, musculoskeletal discomfort, and rash/acne

   ii. <u>Longer Range Risks</u>
   - Mycophenolate mofetil may increase the risk of developing lymphoma (a type of cancer of white blood cells) and other malignancies, particularly of the skin—1%-10%. Participants will be monitored for safety including malignancies during the study. To reduce the chances of skin cancer, participants will be encouraged to wear protective clothing and using an effective sunscreen when exposed to sunlight.
   - In rare cases in conditions (e.g. transplant, Systemic Lupus Erythematosus (SLE)) other than gout mycophenolate mofetil has been linked (incidence rate of 14.4 cases/100,000 person-years and 289/100,000 person-years respectfully) with a serious disorder of the brain known as Progressive Multifocal Leukoencephalopathy (PML). Following discontinuation of MMF patient conditions typically improve with marked reduction of weakness, and in follow-up MRI showed regression of lesions over the next 6 months. We will actively monitor participants and in the event of suspected diagnosis of PML, MMF will be withdrawn.
   - Mycophenolate mofetil use is associated with increased risks of pregnancy loss and congenital malformations.

According to a survey we conducted of the top 40 prescribers of pegloticase (private practice and academic rheumatologists), the majority of physicians reported more enthusiasm for MMF and MTX than leflunomide or azathioprine. While physician-reported enthusiasm for MMF and MTX was equivalent in this survey, the increased concerns about hepato-renal toxicity related to MTX, the potential confounding benefit of leflunomide or MTX in suppressing gouty attacks, as well as the dose and time needed to up-titrate MTX to suppress immune function made MMF the more pragmatic choice.

To our knowledge, this will be the first study to test the hypothesis that immunogenicity to pegloticase can be attenuated via MMF. For this study, we are testing a short course of the immune modulating agent MMF vs PBO to improve treatment efficacy and reduce IR in patients being treated for chronic refractory gout as an innovative approach to gout management with pegloticase. New strategies to deal with the growing burden of gout and to improve use of existing therapies are urgently needed and this proof-of-concept study represents a novel approach addressing both clinical and immunological questions.

5.3 JUSTIFICATION FOR DOSE

For those randomized to the peg+MMF arm we will begin a MMF run-in at 500 mg/twice per day for the first week, and if tolerated titrate the dose up to 1000mg/twice per day for the second week of run-in prior to initial pegloticase infusion. MMF (or matching PBO in the other arm) will be titrated to 1000 mg/twice per day, the standard, well-tolerated dose used in other rheumatic diseases[6] (concurrent with the first pegloticase infusion).

All participants in the study will receive pegloticase at the FDA approved dose of 8 mg administered intravenously every 2 weeks for a total of 6 infusions over a 12-week treatment period, and over an additional 12-week pegloticase opt-in follow-up period (per standard of care).

5.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA) (See section 2.3).

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

6 STUDY POPULATION

6.1 INCLUSION CRITERIA

- Men and women ≥ 18 years of age
- Chronic refractory gout*

*Defined as: Persons whose signs and symptoms are inadequately controlled with urate lowering therapy (e.g. xanthine oxidase inhibitors or uricosuric agents) at a medically appropriate dose or for whom these drugs are contraindicated.

6.2 EXCLUSION CRITERIA

- Weight > 160kg (352.74 lbs.)
- Any serious acute bacterial infection (2 weeks prior to Visit 1), unless treated and complete resolved with antibiotics
- Severe chronic or recurrent bacterial infections (such as recurrent pneumonia, chronic bronchiectasis)
- Current immunocompromised condition, including current or chronic treatment with immunosuppressive agents (prednisone or equivalent dose $\underline{\geq}$ 5 mg/day)

procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:
If the study drug is discontinued, unless the subject withdraws consent, the participant will complete visit 17 (two weeks post discontinuation) and visits 17-20. If the participant doesn't want to continue with the follow-up visit schedule detailed above, then it is important to complete a close-out visit.

Based on the known safety profiles of pegloticase and MMF and the procedures we have in place, we believe it is very unlikely, but possible that we could witness one serious AE related to infection. We will institute a stopping rule for safety re-evaluation that would occur if we register more than one such serious adverse reaction (eg. infection that leads to hospitalization). We would then stop the study to comprehensively review safety and our study protocols in conjunction with the DSMB. Other serious adverse reaction or deaths may or may not be related to the study and stopping or discontinuation of the study will be considered on an individual basis. See **Appendix 9** Data Safety Monitoring Plan.

8.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention for 1 infusion period

The reason for participant discontinuation or withdrawal from the study will be recorded on the Study Closeout/Withdrawl/Termination CRF. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced.

8.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The study coordinator will attempt to contact the participant and reschedule the missed visit within the 10 day window between pegloticase infusions and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record or study file.

Rheumatology at the University of Alabama at Birmingham. All lab samples will be discarded if the participant is deemed not eligible for the study.

Visit 2 - Run-In Visit

- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Review / update concomitant medications
- Gout Flare/tophus assessment
- Blood draw
- Laboratory
    - sUA
    - Urine pregnancy test for premenopausal women
    - CMP
- Randomization will occur at Visit 2/Run-In. Dispense 2 week course of MMF (500mg/twice per day for the first week, and 1000mg/twice per day for the second week of run-in) or placebo, with dosing instructions per randomization assignment.
- Gout Flare Prophylaxis

Participants will be placed on a prophylactic regimen of colchicine or NSAID to prevent gout flares, unless medically contraindicated or not tolerated, and will receive this prophylaxis for at least two weeks prior to the first administration of pegloticase. Gout flare prophylaxis will continue for the duration of the study unless medically contraindicated or not tolerated.

Visit 3 (Baseline-0 weeks)

Visit 3 will occur within 2 weeks of the run-in visit.
The markers for the study primary and secondary outcomes will be collected at each visit. Other data will be collected as needed for safety monitoring.

- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Review / update concomitant medications
- Assess any AEs, and record
- Gout Flare assessment
- Assess compliance (via pill count) and dispense course of MMF (1000 mg/twice per day) or PBO, with dosing instructions
- PROs (PROMIS-29 & GIS instrument)
- Targeted Physical Exam and joint assessment
- Laboratory
    - CBC with diff
    - IgG
    - sUA
    - Pregnancy test for premenopausal women
    - CMP
    - MMF adherence
    - Pegloticase Antibody/Mechanistic Study
- Gout Flare Prophylaxis
- IR Prophylaxis / Assess for IRs
- Administer pegloticase infusion, per site guidelines

infusion of pegloticase will be defined as an AE. Other cases that occur outside of the 2-hour window may also be categorized as an IR as per site PI discretion.

- Anaphylaxis will be defined using the National Institute of Allergy and Infectious Diseases (NIAID)/ Food Allergy and Anaphylaxis Network (FAAN) criteria: acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives; pruritus or flushing; urticarial, and angioedema (of lips, tongue, or uvula) and at least one of the following:
  - Hypotension (i.e., systolic blood pressure < 90 mm Hg or > 30% decrease from that person's screening) or associated symptoms of end-organ failure (e.g., hypotonia [collapse], syncope, incontinence)
  - Respiratory compromise (e.g., dyspnea, bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

Expected potential AEs Associated with Colchicine (see also section 2.3.1)

Participants taking colchicine for gout flare prophylaxis may experience gastrointestinal intolerance which may lead to nausea, persistent diarrhea, and/or gastrointestinal bleeding. The most commonly reported side effects for the prophylaxis of gout were diarrhea (23%) and pharyngolaryngeal pain (3%).

Other rare AEs associated with colchicine include:

- Neutropenia, leading to an increased risk of infection
- Anemia
- Myalgia or myositis
- Alopecia
- Pruritus
- Neuropathy
- Oligospermia

While taking colchicine participants should avoid eating grapefruit and Seville oranges or drinking grapefruit juice or Seville orange juice. Consumption can increase their chances of experiencing serious side effects.

9.3.3.4 DEFINITION OF UNEXPECETED ADVERSE EVENTS (SAE)

An adverse event will be considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if it is not consistent with the risk information described in section 9.3.3.3 of this study protocol.

9.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by the study monitor (see section 11.1.7).

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (eCRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study drug will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of

9.4.2 UNANTICIPATED PROBLEM REPORTING

To ensure that appropriate steps are taken in a timely manner to protect other participants from avoidable harm, we will adhere to HHS regulations at 46.103(b)(5) and will promptly report unanticipated problems to the IRB, NIAMS, FDA, appropriate institutional officials, any supporting department or agency head (or designee), and OHRP.

- Unanticipated problems that are serious adverse events should be reported to the IRB, NIAMS, FDA etc. within 24 hours of the investigator becoming aware of the event.
- Any other unanticipated problem should be reported to the IRB, NIAMS, FDA etc. within 10 business days of the investigator becoming aware of the problem.

9.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be informed about unanticipated problems, and study-related results on an individual or aggregate level.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint(s):
Assess the feasibility of a short course of immune modulating therapy with daily mycophenolate mofetil (MMF). We will start to test the hypothesis that MMF for 12 weeks will safely attenuate immunogenicity conferred by pegloticase as determined by the proportion of participants achieving and maintaining a serum urate ≤ to 6 mg/dL through 12 weeks, compared to concurrent controls. After 12 weeks of co-administration, all participants will continue on pegloticase for an additional 12 weeks without combination MMF therapy to evaluate the durability and safety of this approach

Primary Safety Endpoint(s):
Assess the incidence and types of adverse events /infusion reactions.

Secondary Endpoints:
1) Determine the 6 month durability of immune modulation after discontinuation of the short course of MMF by: a) assessing the absolute change in serum urate from baseline to Week 24, and Week 12 to Week 24, and b) determining the proportion of participants with serum urate ≤ 6 mg/dL through 24 weeks, and Week 12 to Week 24; 2) Identify and characterize the pegloticase immune response by immunoglobulin isotypes (IgG and IgM), specificities, and antibody titer, and 3) Examine patient reported outcomes (PROs) using the National institute of Health (NIH) supported Patient Reported Outcomes Measurement Information System (PROMIS) and Gout Impact Scale (GIS) instruments.

10.2 SAMPLE SIZE DETERMINATION

As a pilot proof of concept study, we are not able to fully power the trial to detect a difference between a rate of 60% success vs the success rate after induction by MMF, which we hypothesize will be 80% or more. If we powered the study with 80% power, 2 sided type I error of 5%, we would require 82 participants per group to demonstrate this difference with a treatment and control group. To ensure resources are not wasted, we will confirm that a future larger study is worth pursuing based on results of this pilot study. We have included a decision table based on Fisher's exact tests to define how results will inform our decision about a future full scale study (see section 10.4.1).

10.3 POPULATIONS FOR ANALYSES

The analysis population will include all enrolled participants who received at least 1 dose of study medication (mycophenolate mofetil or placebo) during treatment period (modified intention to treat, mITT). The protocol

averaging and multiple imputation based on the average of the flanking values. The utility of this approach will necessarily depend on the type of missing data and the pattern of the flanking values. In cases where imputation is deemed appropriate, PROC MI /PROC MIANALYZE (SAS Institute Inc., Cary, NC) will be used. We will generate five replicates of the event or outcome of interest and redo the assessments. For secondary and exploratory outcomes, we will use similar approaches. We will use propensity score matching (which reduces the cohort by any mismatches and thus is different than covariate adjustment) to assess the impact of the missingness mechanism. We will examine the sensitivity of the conclusions to any missingness found.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1.1 INFORMED CONSENT PROCESS

11.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol.

11.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Participants will be asked to read and review the UAB IRB approved consent forms (see MOOP section 2.f). The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, NIAMS, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRBs, and NIAMS and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

UAB	University of Alabama at Birmingham
ULT	Urate Lowering Therapy
USP	United States Pharmacopeia
UM	University of Michigan

11.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2.0	02/14/2018	• Updated objects	• Request of NIAMS/KAI
3.0	03/12/2018	• Updated page numbers • Updated section 2 to match section 4 for consistency • Corrected fasting before infusion • Detailed unblinding process • Updated abnormal lab values as AEs • Defined Unanticipated AE (UAE) • Updated timing of SAE reporting. • Fixed typo • Clarified definition of population and planned analysis • Updated timing of reporting of protocol deviations.	• Request of NIAMS/KAI • Request of NIAMS/KAI to address inconsistency in text • Request of NIAMS/KAI to address a discordance in text. • Request of NIAMS/KAI to address events that would lead to unblinding and reporting to NIAMS/KAI/DSMB • Request of NIAMS/KAI to revise the protocol to include all abnormal lab values or test results at AEs • Request of NIAMS/KAI to provide definition of UAE • Request of NIAMS/KAI to specify that NIAMS and the DSMB via KAI will be updated within 48 hours • Request of NIAMS/KAI to correct the typo in section 10.1 • Request of NIAMS/KAI to identify and further describe the analysis datasets • Request of NIAMS/KAI to specify that NIAMS and the DSMB via KAI will be notified within 48 hours of protocol deviations
4.0	3/21/2018	• Added text to specify all SAE regardless of relatedness will be reported to the NIAMS and DSMB via KAI w/in 48 hours	• Request of KAI/NIAMS
5.0	06/19/2018	• Updated study roster	• Rachel Burrell, PharmD has moved to part-time status. Add Chris Chapleau as lead UAB pharmacist
6.0	07/12/2018	• Start participants on MMF/placebo 500mg/twice a day for the first week, and if tolerated titrate the dose up to 1000mg/twice a day for the second week of run-in prior to the first	• To ensure tolerability to MMF and identify potential MMF intolerance earlier • Collection of CBC at run-in is unnecessary as it will be collected