REDUCING IMMUNOGENICITY TO PEGLOTICASE (RECIPE)

National Clinical Trial (NCT) Identified Number: NCT03303989
Principal Investigator: Kenneth G. Saag, MD, MSc
IND/IDE Sponsor: University of Alabama at Birmingham
Funded by: National Institute of Arthritis and Musculoskeletal and Skin Diseases and Horizon Pharma, PLC
Version Number: 12.0
01/13/2020

Table of Contents

1 STATEMENT OF COMPLIANCE

The REduCing Immunogenicity to PegloticasE (RECIPE) trial will be conducted in accordance with the International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Terms and Conditions of Award. The Principal Investigator (Kenneth Saag, MD, MSc) will ensure that no deviation from, or changes to the protocol will take place without prior agreement from the NIAMS, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials have been submitted and approved by the University of Alabama at Birmingham (UAB) Institutional Review Board (IRB) and vetted with the Food and Drug Administration (FDA) per the investigation new drug (IND) review. Any amendment to the currently approved protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; in be obtained from any participants who provided consent, using a previously approved consent form.

2 PROTOCOL SUMMARY

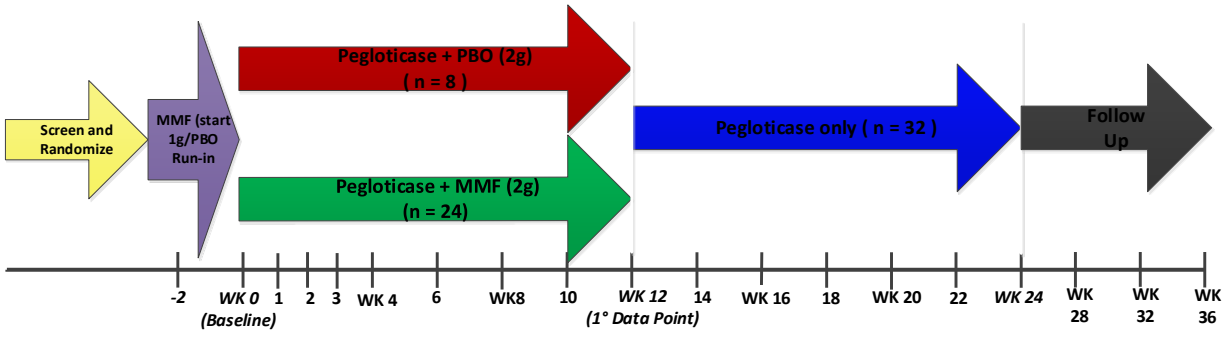
2.1 SYNOPSIS

Title:	Reducing Immunogenicity to Pegloticase (RECIPE)
Study Description:	Pegloticase treatment for chronic refractory gout is limited by immunogenicity. The investigators propose the REduCing Immunogenicity to PegloticasE (RECIPE) trial to investigate the question of whether a short course of immune modulating therapy with mycophenolate mofetil (MMF) can significantly and safely attenuate immunogenicity to pegloticase and ensure patients afflicted with chronic refractory gout have better treatment outcomes and improved quality of life.
Objectives:	Evaluate feasibility and preliminary efficacy and safety of a short course of immunosuppressive therapy to prevent immunogenicity conferred by pegloticase.
Endpoints:	Primary Endpoints: The co-primary aims of our proof-of-concept double-blind study are to first assess the feasibility and preliminary efficacy of a short course of immune modulating therapy with daily mycophenolate mofetil (MMF). We will explore the future full-scale study hypothesis that administering MMF for 12 weeks can safely attenuate immunogenicity conferred by pegloticase as determined by the proportion of participants achieving and maintaining a serum urate (sUA) ≤ to 6 mg/dL for 12 weeks, compared to concurrent controls. After 12 weeks of co-administration of MMF with pegloticase or placebo, all participants will continue on pegloticase for an additional 12 weeks without combination MMF therapy to evaluate the longer-term benefits and safety of this approach. The second co-primary safety aim will assess the incidence and types of adverse events/infusion reactions potentially associated with MMF. 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.
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



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).

3 INTRODUCTION

3.1 STUDY RATIONALE

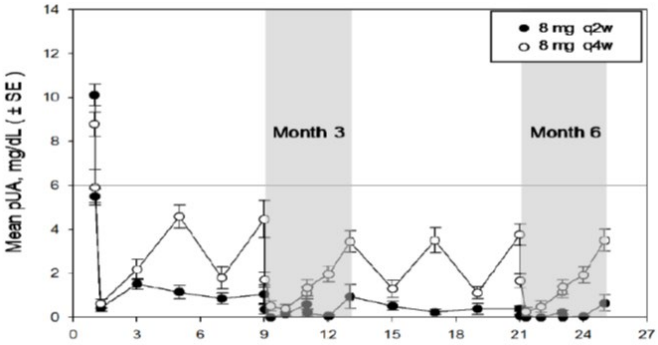
Pegloticase, a recombinant modified mammalian urate oxidase (uricase), that is approved by the Food and Drug Administration (FDA) and the European Commission for use in gout patients is very efficacious in reducing serum urate (**Figure 2**) and improving clinical signs and symptoms of gout, such as 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

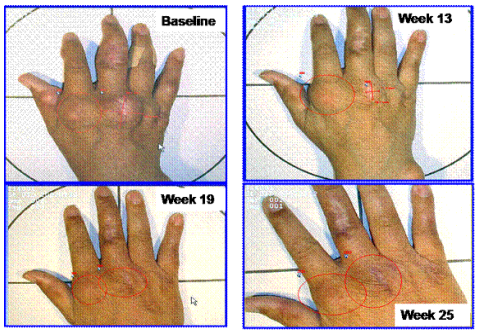
Gout affects approximately 4% of the U.S. population, is the most common form of inflammatory arthritis in men, and is associated with decreased quality of life.[7-9] The frequency of gout is increasing worldwide, with prevalence rates estimated to be as high as 7% in older men, based on our work and 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]

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.

b. Pegloticase (Infusion)

i. Immediate Risks

It is common for potent urate lowering therapies to lead to acute attacks of gout. Other uncommon symptoms reported in at least 5% patients treated with pegloticase that may occur during the study period are ecchymoses, sore throat, constipation, chest pain, and vomiting. Serious allergic reactions may happen in some people while receiving infusion of pegloticase. These infusion reactions can be serious and usually happen within 2 hours of the infusion. Chest discomfort (15%), flushing (12%), and dyspnea (11%) are the most common symptoms. Symptoms associated with pegloticase infusion resolve with slowing, interrupting, or stopping the infusion. 91% of these symptoms occur in patients with serum urate concentrations greater than 6 mg/dL. Therefore, all participants serum urate will be checked prior to infusion and any participant with 2 or more serum urate test > 6 mg/dL (following initial infusion) will not be infused and will be removed from the study. Symptoms associated with infusion reactions include:

- Hemolysis; Individuals with G6PD deficiency are excluded from the study
- Join pain - 14%; Pain following injection. Pain subsides over time
- Difficulty breathing - 14%; Subsides over time
- Muscle spasms - 14%; Subsides over time
- Nausea - 9%; Subsides over time
- Fever - 14%; Subsides over time
- Back pain - 14%; Subsides over time
- Diarrhea - 14%; Subsides over time
- Erythema - 14%; Subsides over time
- Hypersensitivity - 14%; Subsides over time
- Rash - 29%; Subsides over time
- Pain/bruising at the infusion site; Pain following injection and bruising will subside over time.
- Gout flares also known as gout attacks; Participants will be placed on a NSAID and/or colchicine regimen to help manage pain/discomfort. Flare/attack will subside over time
- Other symptoms, occurring at rates of 2% to 5%, included dizziness (5%), vomiting (5%), pain (4%), chills (3%), hypertension (3%), hypotension (3%), tachycardia (3%), feeling hot (2%), musculoskeletal discomfort (2%), and wheezing (2%)
- Participants will be observed for any signs of a serious allergic reaction during and after the treatment with pegloticase for infusion reactions
- Pegloticase has not been formally studied in patients with congestive heart failure, but some patients in clinical trials have experienced exacerbation. Patients who have diagnosed congestive heart failure will not be enrolled in the study

ii. Longer Range Risks

- The risks to pregnant women or an unborn baby when taking pegloticase is not fully known.

c. Colchicine (Oral Ingestion for flare prophylaxis)

i. Immediate Risks

- The most commonly reported side effects for the prophylaxis of gout with colchicine was diarrhea (23%) and sore throat pain (1%-10%). These symptoms subside over time following discontinuation of colchicine.
- In rare case (1-10%) more serious gastrointestinal bleeding may occur. Participant's with known gastrointestinal problems, such as a peptic ulcer or colitis, will be advised to consult with study doctor and their doctor before taking colchicine.
- All participants will be instructed not to ingest/drink grapefruit and Seville oranges or to drink grapefruit juice or Seville orange juice.

ii. Long Range Risks

- Colchicine has been associated in animal reproduction studies as having an adverse effect on the fetus, however there are no adequate and well-controlled studies in humans.

3.3.2 KNOWN POTENTIAL BENEFITS

Previous clinical trials have demonstrated the significant disease-modifying benefits of pegloticase given every 2 weeks (tophus resolution, reduced flare frequency, reduction in tender joint coutn (TJC), and improved patient-reported outcomes in pain, physical function, and quality of life (QOL)) were demonstrable within 6 months.[5,19-22] Pegloticase provides medical benefits by lowering sUA and by eliminating tophi in these patients chronic gout who are refractory to conventional therapy, and therefore have limited or no therapeutic options. If the RECIPE study is successful and determines that mycophenolate mofetil can safely and effectively attenuate immunogenicity to pegloticase it will provide evidence for a larger clinical trial, and ultimately may provide a new strategy to help persons with chronic gout achieve better health-related outcomes.

Participant's gout may improve while participating in this study, however this cannot be guaranteed. There may be no direct benefit to participants participating in this study.

3.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

A potential benefit from this study is that the knowledge gained could provide valuable information about gout and its treatments, providing evidence to justify a larger study that may help others with gout in the future. If successful, the study results may contribute towards a safer, more effective treatment of gout.

We will take following precautions to avoid/minimize risks to the participants:

All participant lab data and responses to questionnaires will be captured during scheduled study visits. All data will be entered into coded electronic case report forms (CRF) (study ID and clinic ID only), and will be checked by study personnel daily for accuracy. On a quarterly basis study investigators and staff will review GCP, human subject's protections/confidentiality, and study procedures. The history, physical examination and review of laboratory data will be conducted by the principal investigator or co-investigator, all of whom are experienced in clinical trials. The research team will meet biweekly to review recruitment, enrollment, laboratory tests, source documents, and electronic case report forms. In the event an adverse event occurs this will be reported to the UAB IRB at the time of continuing review. All serious adverse events (SAEs) will be reported to the IRB, KAI, and NIAMS within 48 hours of the Principal Investigator becoming aware of the event. All study staff members will be informed by the PIs about any unanticipated problems involving risks to the participant. If any protocol changes are needed, the PIs will submit a modification request to the IRB. Protocol changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research participant. In such cases, the IRB will be promptly informed of the change following implementation (within 1 week).

The safety of the study participants is the highest priority for this project therefore an independent data safety monitoring board will be appointed and will be responsible for evaluating the scientific issues related to the study. The Data Safety Monitory Board (DSMB) will receive data periodically (e.g. every 6 months) including any pre-specified time points. The outcome of each patient is the top priority and as such, a process for the ongoing monitoring of results by independent scientists is important to maintain throughout the duration of the project. The DSMB may recommend at any point that the study be stopped if the risk-benefit assessment for continuance is deemed unfavorable.

4 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess efficacy of daily mycophenolate mofetil (MMF) to attenuate immunogenicity to pegloticase.	Proportion achieving and maintaining serum urate ≤ 6 mg/dL through 12 weeks, compared to concurrent controls.	Serum urate ≤ 6 mg/dL is slightly below the urate solubility threshold and this threshold has been the accepted standard for nearly all modern gout trials.[23-26] If the serum urate goal is not maintained before or at the 12 week mark, it will be assumed that the participant has developed clinically relevant anti-pegloticase antibodies and they will receive no further infusions. This assumption and subsequent discontinuation of pegloticase is consistent with the protocol of large phase III randomized controlled trials and the product label.
To assess the incidence and types of adverse events/infusion reactions potentially associated with a dual therapy regimen of pegloticase and MMF.	Incidence and Type of Adverse Events (AEs), Serious Adverse Events (SAEs), and Participant withdrawals due to AEs, anaphylaxis, and Infusion Reactions (IRs)	Safety profile is important because of the addition of an immune modulatory agent (MMF) that has potential of causing serious AEs
Secondary		
To assess durability of immune modulation after discontinuation	Absolute change in serum urate from baseline to wk 24; week 12 to 24 Proportion of participants with serum urate ≤ 6 mg/dL through week 24; week 12 to 24	Assess if the efficacy of the short course of MMF continues following discontinuation.
To identify and characterize pegloticase immune response by immunoglobulin	Anti-pegloticase antibody isotypes (IgG/IgM), specificity, and titers	We anticipate that the primary Ab produced will be IgM anti-pegloticase but some participants, who will likely be the non-

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]

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)

- Participants at risk for tuberculosis (TB). Specifically, participants with: i) current clinical, radiographic or laboratory evidence of active or latent TB; ii) a history of active TB within the last 3 years even if it was treated; iii) a history of active TB greater than 3 years ago unless there is documentation that the prior anti-TB treatment was appropriate in duration and type
- Known history of Hepatitis B surface antigen-positive or Hepatitis B DNA positive participants.
- Known history of Hepatitis C RNA-positive participants
- Human Immunodeficiency Virus (HIV) infection positive
- G6PD deficiency (tested at Screening/Visit 1)
- Severe chronic renal impairment (glomerular filtration rate [GFR] <25 mL/min/1.73 m2) or currently on dialysis
- Participants having any transplant surgery requiring maintenance immunosuppressive therapy
- Non-compensated congestive heart failure, uncontrolled arrhythmia, treatment for acute coronary syndrome (myocardial infarction or unstable angina), or hospitalization for congestive heart failure within 3 months of screening or uncontrolled blood pressure (>160/100 mm Hg) at baseline (Screening/Visit 1 and Week 0/Visit 3)
- Pregnant, planning to become pregnant, breast-feeding, or not on an effective form of birth control (defined in Section 8.3.8.2, see MOOP Section 2.f.2 Informed Consent)
- Prior treatment with pegloticase, another recombinant uricase, or concomitant therapy with a polyethylene glycol (PEG)-conjugated drug
- Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product
- MMF treatment is contraindicated or considered inappropriate
- Recipient of an investigational drug within 4 weeks prior to study drug administration or plans to take an investigational agent during the study
- Current liver disease as determined by alanine transaminase ALT or aspartate transaminase (AST) levels >3 times upper limit of normal
- Currently receiving treatment for ongoing cancer, excluding non-melanoma skin cancer
- History of malignancy within 5 years other than skin cancer or *in situ* carcinoma of cervix
- Uncontrolled hyperglycemia with a plasma glucose value >240 mg/dL at screening
- Diagnosed osteomyelitis
- Individuals with hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome
- Not good candidate for the study based on opinion of an Investigator (e.g., cognitive impairment) that might create undue risk to the participant or interfere with the participant's ability to comply with the protocol requirements, or to complete the study**.**

6.3 LIFESTYLE CONSIDERATIONS

Participants will be instructed to discontinue any other medications for the treatment of their gout (e.g. allopurinol), and to refrain from drinking excessive amounts of alcohol (no more than 2 drinks per day), taking any illegal substances during this study, and eating or drinking grapefruit. Participants will not be fasting on the day of infusion; they will be encouraged to have a snack or normal meal 1 hour before, or immediately after, the infusion. As colchicine will be provided for flare prophylaxis all participants will be instructed not to ingest/drink grapefruit and Seville oranges or to drink grapefruit juice or Seville orange juice while participating in RECIPE.

Participants will also be advised to stop taking drugs such as proton-pump inhibitors, calcineurin inhibitors, and probenecid during their time in the study.
Finally, participants will be instructed to not donate blood while participating in the study and for up to one month after they have completed the study.

In the event, a participant declines/refuses to comply with these instructions (e.g. resumes prior urate lowering therapy [ULT] therapy) they will be withdrawn from the study.

6.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in RECIPE but are not subsequently randomly assigned to the study intervention or entered in the study. We will collect a minimal set of screen failure information to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria. Individuals who do not meet the criteria for participation in this trial (screen failure) because of an abnormal lab value may be rescreened. Rescreened participants will be assigned a new participant number, but will be documented in the system as a rescreen.

6.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Participant Recruitment

We will recruit and enroll 32 adults (≥ 18 years of age) 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. Recruitment will occur at UAB and UM. Patients will also be recruited directly from the UAB/UM hospitals and outpatient care facilities (e.g. UAB/UM Rheumatology Clinics each seeing greater than 1000 gout patients per year). Advertisements will be placed in the web page www.researchmatch.org, Birmingham/Ann Arbor metro area local newspapers, and UAB/UM campus publications. The inclusion and exclusion criteria will be reviewed with all potential participants, and informed consent will be obtained by the principal investigator, one of the co-investigators, or a trained member of the study staff. Study procedures will not begin until signed informed consent has been obtained.

The study investigators and staff will have meetings bi-weekly to monitor site recruitment and to determine any intervention for poor recruitment. In the event a problem is identified by either study site PI or staff, a teleconference/webinar will be scheduled to review the issue. These teleconferences/webinars will include discussions of overall recruitment status and identified barriers to recruitment experienced by the site with the study team

Participant Retention

During the screening and enrollment process, contact will be made with participants in a variety of ways (letters, staff contact by phone and in person) for optimal retention. To increase retention, we hire engaging, attentive, and responsive staff and who work with patients to provide flexible apt times where needed. The following major principals and commonly used strategies to maximize retention and minimize loss to follow-up will be employed during the trial:

- Stressing the idea that participants have an active role in the research and are part of the research team
- Enhancing participant's understanding of the study's mission and the protocol
- Stressing that retention efforts begin with recruitment and are an ongoing process
- Building participant relations and participant satisfaction, with the study staff taking a central role on this effort
- Emphasizing the importance of congeniality, respectfulness and friendliness in interactions with participants
- Actively discuss with participants any questions and concerns pertaining to their condition
- Identifying potential problems and key retention factors, and developing intervention strategies regarding retention
- Assessing each participant's drop out potential and intervening as needed to keep participant interested in continuing to participate

In the event a study participant does not return for a study visit, then the site study staff will call to reschedule visit.

7 STUDY INTERVENTION

7.1 STUDY INTERVENTION(S) ADMINISTRATION

7.1.1 STUDY INTERVENTION DESCRIPTION OVERVIEW

Participants will be randomized 3:1 to either pegloticase + MMF (Peg+MMF) or to pegloticase + placebo (peg+PBO).

Experimental Arm:
Participants randomized to this arm will receive pegloticase + mycophenolate mofetil.

Drug: Mycophenolate Mofetil
Participants randomized to the pegloticase + MMF arm will start on 1) Pegloticase 8 mg intravenously (IV) every two weeks, and 2) mycophenolate mofetil at 500 mg/BID and titrating up to 1000 mg/BID in 2 weeks if tolerated. Mycophenolate mofetil therapy will continue for 12 weeks at the highest tolerated dose. After the 12-week combination mycophenolate mofetil and pegloticase study period, participants will continue open-label pegloticase therapy for an additional three months.

Drug: Pegloticase 8 mg/mL [Krystexxa]
Participants randomized to the pegloticase + MMF arm will start on 1) Pegloticase 8 mg IV every two weeks#, and 2) mycophenolate mofetil at 500 mg/BID and titrating up to 1000 mg/BID in 2 weeks if tolerated. Mycophenolate mofetil therapy will continue for 12 weeks at the highest tolerated dose. After the 12-week combination mycophenolate mofetil and pegloticase study period, participants will continue open label pegloticase therapy for an additional three months.
Other Name: Krystexxa

Placebo Comparator Arm:
Participants randomized to this arm will receive pegloticase + placebo

Drug: Placebo
Participants randomized to the pegloticase + placebo will receive placebo instead of mycophenolate mofetil therapy for 12 weeks. After the 12-week combination placebo and pegloticase study period, participants will continue open label pegloticase therapy for an additional three months.

Drug: Pegloticase 8 MG/ML [Krystexxa]
Participants randomized to the pegloticase + placebo will receive placebo instead of Mycophenolate mofetil therapy for 12 weeks. After the 12-week combination placebo and pegloticase study period, participants will continue open label pegloticase therapy for an additional three months.
Other Name: Krystexxa

7.1.2 DOSING AND ADMINISTRATION OF STUDY DRUGS

Mycophenolate Mofetil (MMF)

Patients will be instructed that oral dosage tablets (250 mg over-encapsulated MMF or PBO) will be administered on an empty stomach (1 hour before or 2 hours after meals) to avoid variability in Moiety Mycophenolic Acid (MPA) absorption. If a dose is missed, it will be administered as soon as it is remembered. If it is close to the next scheduled dose, the participant will be instructed to skip the missed dose and resume at the next regularly scheduled time; thus, participants will be instructed not to double a dose to make up for a missed dose.

Pegloticase

Pegloticase will be administered (per FDA approved guidelines) as an admixture of 8 mg in 250 mL of 0.45% or 0.9% Sodium Chloride Injection, USP for IV infusion over a target infusion time of 120 minutes by gravity feed or infusion pump. Pegloticase will not be administered as an IV push or bolus. Standardized IR prophylaxis consisting of pre-treatment with antihistamines and corticosteroids will accompany each infusion. The drug name, dose, and timing of these prophylactic medications will be recorded.

Participants will not be fasting on the day of infusion; they will be encouraged to have a snack or normal meal 1 hour before, or immediately after, the infusion. Prior to pegloticase infusion participants will receive infusion prophylaxis (e.g. oral fexofenadine (60 mg) the night before and fexofenadine (60 mg/PO) and acetaminophen (1000 mg/PO) the morning of the infusion; and hydrocortisone IV (200 mg) immediately prior to the infusion).

In a patent IV site, using tubing with no in-line filter, the drug preparation will be infused over approximately 120 minutes (within ± 15 minutes) while the participant is under close observation for any signs of distress. Administration of drug will be immediately discontinued if respiratory distress, agitation, chest or back pain, urticaria, or another clinically significant event occurs during infusion. If the adverse event (AE) meets the definition of an serious adverse event (SAE), the infusion may not be restarted under any circumstances. A SAE will be reported within 24 hour or sooner to the Data Safety Monitoring Board (DSMB). If the AE does not meet the definition of an SAE, the site PI may make the decision to re-start the infusion depending upon the nature and severity of the AE.

Infusions subsequent to an infusion-related reaction in an individual participant may be given in a larger volume of diluent, not to exceed 500 mL. In such a case, the infusion duration will also be extended to a minimum of 3 hours. The total volume and duration of infusion will be captured in the medical record and CRF.

As a precaution, emergency equipment will be readily available to treat a possible hypersensitivity reaction, and will include drugs that would be used to treat an anaphylactic reaction. Personnel fully trained in advanced cardiopulmonary resuscitation and in the use of the emergency equipment will be readily available during, and for 1 hour after, the infusion. At the end of the infusion, the IV line will be flushed with 10 mL of normal saline to assure the full dose is administered. As IRs can occur after completion observation of participants for approximately an hour post-infusion will be performed.

7.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY OF STUDY DRUGS

7.2.1 ACQUISITION AND ACCOUNTABILITY

Pegloticase will be shipped by Horizon Pharma, PLC to the study sites. The UAB IDS Pharmacy will be responsible for the storage, over-encapsulation, and shipment of mycophenolate mofetil and placebo pills for this study. MMF will be purchased in bulk quantity through the UAB Investigational Drugs Pharmacy, which will also oversee the process of over-encapsulation with cellulose of the active medication and placebos, handle medication storage, distribution, and assignment of randomization sequence. A drug log will be used to track the study drug from pharmacy to each randomized study participant. The centralized management of the medication will allow maintenance of a double-blind trial. 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. Further questions about pharmacy activities can be directed to: Chris Chapleau, PharmD; IDS Pharmacy, University of Alabama at Birmingham Hospital, 205-934-7191.

Supplies and medication vials used in preparing medications will be discarded as waste immediately after product preparation. The waste is incinerated on-site at UAB Hospital and UM hospital. In addition, incineration is the method of destruction for expired, returned and unused product at study closure. When a study is closed or closed to enrollment (and no participants are being treated), sites will have 60 days to document destruction of unused product.

7.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Mycophenolate Mofetil (MMF)
MMF, the immune modulator for the study, is the 2-morpholinoethyl ester of moiety mycophenolic acid (MPA), and is an inosine monophosphate dehydrogenase (IMPDH) inhibitor. The chemical name for MMF is 2-morpholinoethyl (E)-6-(1,3-dihydro- 4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$. MMF will be purchased by UAB from Besse Medical (West Chester Township, OH). MMF capsules include croscarmellose sodium, magnesium stearate, povidone (K-90) and pregelatinized starch. The MMF capsule shells contain black iron oxide, FD&C blue #2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide. All MMF capsules will be over-encapsulated with cellulose to match compounded placebo. Favorable pharmacokinetic properties of the encapsulation process have been consistently noted with other substances. Blinded study drug labeling will be annotated with the protocol number by the research pharmacist. The UAB site pharmacy will maintain an inventory of drug supplies received and dispensed.

Pegloticase

Pegloticase (Krystexxa®) is a clear, colorless, sterile solution in phosphate-buffered saline intended for IV infusion after dilution and will be supplied by Horizon Pharma, PLC. Pegloticase is commercially available in the US in a single-use, 2 mL glass vial with a Teflon coated (latex-free) rubber injection stopper. Each mL of pegloticase contains 8 mg of uricase protein conjugated to 24 mg of 10 kDa monomethoxypoly (ethylene glycol). Excipients include disodium hydrogen phosphate dihydrate, sodium chloride, sodium dihydrogen phosphate dehydrate, and water for injection. All participants in the study will receive pegloticase at the same dose of 8 mg administered IV 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). Study drug labeling will be annotated with the protocol number.

7.2.3 PRODUCT STORAGE AND STABILITY

Mycophenolate Mofetil (MMF)
MMF has demonstrated teratogenic effects in rats and rabbits, therefore MMF tablets should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in MMF tablet/capsules.

Pegloticase
Before preparation for use, pegloticase will be stored in the carton, maintained under refrigeration between 2ºC and 8ºC (36ºF and 46ºF), protected from light, and will not be shaken or frozen. Investigational clinical supplies will be received by a designated person at each study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated assistants have access. Clinical supplies will be dispensed only in accordance with the protocol. We will keep accurate records of the clinical supplies received and, the amount dispensed for each participant, and the amount remaining at the conclusion of the study. We will mark the label of any vials that are not to be used with a large “X,” and document the reason for rejecting them on the drug accountability log. In accordance with good pharmacy practice, gloves will be worn during preparation of the dose.

7.2.4 PRODUCT DESTRUCTION

The study sites will maintain an inventory of drug supplies received and dispensed. UAB will provide forms to document all inventory transactions. Upon completion or termination of the study, all unused drug supplies, will be destroyed with written certification confirming destruction within sixty (60) days of study completion or expiration of the study drug.

7.2.5 PREPARATION

Mycophenolate Mofetil (MMF)
Mycophenolate Mofetil (MMF) capsules include croscarmellose sodium, magnesium stearate, povidone (K-90) and pregelatinized starch. The MMF capsule shells contain black iron oxide, FD&C blue #2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide. All MMF capsules will be over-encapsulated with cellulose to match compounded placebo. Favorable pharmacokinetic properties of the encapsulation process have been consistently noted with other substances.

Pegloticase
Pegloticase vials will be visually inspected for particulate matter and discoloration before administration, whenever solution and container permit. Vials will not be used if either is present. Using appropriate aseptic technique, 1 mL of pegloticase will be withdrawn from the vial into a sterile syringe. Any unused portion of product remaining in the vial will be discarded. Syringe contents will be injected into a single 250 mL bag of 0.45% or 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) for IV infusion and will not be mixed or diluted with other drugs. The infusion bag containing the dilute pegloticase solution will be inverted a number of times to ensure thorough mixing, but will not be shaken. Pegloticase-diluted in infusion bags is stable for 4 hours at 2°C to 8°C (36°F to 46°F) and at room temperature (20°C to 25°C, 68°F to 77°F); however, the diluted solution will be stored under refrigeration, not frozen, protected from light, and used within 4 hours of dilution. Before administration, the diluted solution of pegloticase will be allowed to reach room temperature. Pegloticase in a vial or IV infusion fluid will never be subjected to artificial heating.

7.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be randomized 3:1 to either pegloticase + MMF (Peg+MMF) or to pegloticase + placebo (peg+PBO). Randomization allocation will be balanced in time and by site to achieve 24 peg+MMF and 8 peg+PBO using a double-blind design. Treatment assignment will be determined by a random number generator and stratified by site using a central randomization system to ensure the 24/8 allocation. If any concerns arise during the randomization procedures, both the pharmacist and study coordinator will contact the Data Coordinating Center (DCC) at UAB. The UAB IDS will be responsible for assignment of randomization sequence. A drug log will be used to track the study drug from pharmacy to each randomized study participant. The centralized management of the medication will allow maintenance of a double-blind trial.

As all participants and study investigators will be blinded to treatment assignment. If there is a serious adverse event, then unblinding will be discussed and if deemed necessary to unblind the participant, then the ID of the unblinded participant, reasons for unblinding, name of the pharmacist and a list of whomever becomes unblinded will be kept in the study binder and centrally at the Data Coordinating Center and Central Pharmacy. The pharmacist will contact that participant's primary physician about the exposure. If necessary, the participant will be withdrawn from the study. NIAMS and the DSMB via KAI will be informed of any unexpected unblinding via email or at the scheduled DSMB meetings.

7.4 STUDY INTERVENTION COMPLIANCE

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

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.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

- Based on our competitive enrollment of this study in the event a participant is lost to follow-up, withdraws consent and discontinues the study before the end of week 12 and is therefore unable to contribute to the primary outcome, the enrolling site will be afforded the opportunity to enroll a replacement participant.

9 STUDY ASSESSMENTS AND PROCEDURES

This study will be coordinated by the University of Alabama at Birmingham (UAB). All study visits and procedures will be performed at the United States, at UAB, the University of Michigan, and up to 6 to be named sites. Enrollment will be competitive between sites. Frequency of study visits and clinical evaluations can be found in **Table 1**. Following the first 12 week dual therapy phase, participants will be given an additional three months of open-label pegloticase only therapy (see **Figure 1**) and will be followed to better understand the long-term efficacy (durability) of this approach, which is essential for future studies. Specifically, we will whether assess the durability of the short course of MMF continues over the next 12 weeks in the absence of MMF.

Participants will be seen according to schedule of visits and evaluations outlined in **Table 1** and per the details that follow:

Visit 1 - Screening Visit

The screening visit will take approximately 1 hour to complete. Potential participants will be screened to determine if they satisfy all inclusion and exclusion criteria. Men and women 18 years of age or older will be invited to proceed with informed consent (IC) and enroll in the study. At the screening visit, the study objectives will be explained to potential participants. After all questions raised by a potential participant are answered, and before any protocol-specified screening procedures are initiated, they will be offered the IC for the screening evaluation. A copy of the signed and dated IC form must be provided to the participant. After IC is obtained, a participant number will be assigned. All screening procedures must be completed and eligibility criteria met prior to start of immune-modulating therapy and pegloticase infusions. Basic demographic information and reason(s) for exclusion must be completed on the specified case report form (eCRF) pages for all participants who signed an ICF, but never received pegloticase. During the screening visit, the following procedures will be performed, and information will be obtained to determine eligibility to continue in this research study:

- Review inclusion/exclusion criteria
- ICF
- Date of birth
- Self-reported race/ethnicity
- Medical history that might preclude study participation
- Gout history and symptom severity
- Medication review
    - Medication history (including use of over-the-counter medications [eg. aspirin], use of other prescription medications including gout medications)
    - Dietary supplement/vitamin use
- Vital signs
- Physical exam includes, but is not limited to
    - Eye, Head, Ears, Nose, and Throat Exam (HEENT), and Neck
    - Cardiovascular
    - Dermatological

- 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

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

In addition to gout flare prophylaxis all participants will receive infusion prophylaxis throughout the study (e.g., fexofenadine (60 mg PO) the night before and fexofenadine (60 mg PO) and acetaminophen (1000 mg) the morning of the infusion; and hydrocortisone (200 mg IV) immediately prior to the infusion).

Visit 4 (1 week)

Participants will report 1 week following Visit 3 for a blood draw and check of their CBC.

- Laboratory
  - CBC with diff
  - sUA
  - MMF adherence

Visit 5 (2 weeks)

- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Targeted Physical Exam
- Review / update medical history 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
- Laboratory
  - CBC with diff
  - CMP
  - sUA
  - Pregnancy test for premenopausal women
  - MMF adherence
- Gout Flare Prophylaxis
- Administer pegloticase infusion, per site guidelines
- IR Prophylaxis/ Assess for IRs

Visit 6 (3 weeks)

Participants will report 1 week following Visit 3 for a blood draw and check of their CBC.

- Laboratory
  - CBC with diff
  - MMF adherence

Visit 7 (4 weeks)

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Targeted Physical Exam and joint assessment
- Review / update concomitant medications
- Assess any AEs, and record
- Gout Flare assessment
- PROs (PROMIS-29 & GIS instrument)
- Assess compliance (via pill count) and dispense course of MMF (1000 mg/twice per day) or PBO, with dosing instructions
- Laboratory Assessments

- CBC with diff
- CMP
- sUA
- Pregnancy test for premenopausal
- MMF adherence

- Gout Flare Prophylaxis
- IR Prophylaxis /Assess for IRs
- Administer pegloticase infusion, per site guidelines

Visit 8 (6 weeks)

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Targeted Physical Exam and joint assessment
- 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
- Laboratory Assessments
  - 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

Visit 9 (8 weeks)

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

- Gout Flare Prophylaxis
- IR Prophylaxis /Assess for IRs
- Administer pegloticase infusion, per site guidelines

Visit 10 (10 weeks)

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Targeted physical exam
- Review / update concomitant medications
- Assess any AEs, and record
- Gout Flare Assessment
- Assess drug compliance (via pill count) and dispense course of MMF (1000 mg/twice per day) or PBO, with dosing instructions
- Laboratory Assessments
  - CBC with diff
  - CMP
  - sUA
  - Pregnancy test for premenopausal women
  - MMF adherence
- Gout Flare Prophylaxis
- IR Prophylaxis /Assess for IRs
- Administer pegloticase infusion, per site guidelines

Visit 11 (12 weeks)

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Review concomitant medications, and record
- Assess any AEs, and record
- Gout Flare Assessment
- PROs (PROMIS-29 & GIS instrument)
- Assess drug compliance (via pill count)
- Physical Exam and detailed joint assessment
  - HEENT, and Neck
  - Cardiovascular
  - Respiratory
  - Gastrointestinal
  - Musculoskeletal
  - Neurologic
  - Integumentary
  - VS/Measurements
- Laboratory Assessments
  - 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

Following completion of Visit 11 participants will continue on pegloticase for an additional twelve weeks without immune modulating therapy to evaluate the longer term benefits of this approach. In Phase 2 participants will continue with pegloticase infusions every 2 weeks.

Visit 12 (14 weeks)

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Targeted Physical Exam and joint assessment
- Review / update concomitant medications
- Assess any AEs, and record
- Gout Flare assessment
- Laboratory Assessments
    - CBC with diff
    - sUA
    - Pregnancy test for premenopausal women
    - CMP
- Gout Flare Prophylaxis
- IR Prophylaxis / Assess for IRs
- Administer pegloticase infusion, per site guidelines.

Visit 13 (16 weeks)

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Targeted Physical Exam and joint assessment
- Review / update concomitant medications
- Assess any AEs, and record
- Gout Flare Assessment
- PROs (PROMIS-29 & GIS instrument)
- Laboratory Assessments
    - CBC with diff
    - sUA
    - Pregnancy test for premenopausal women
    - CMP
- Gout Flare Prophylaxis
- IR Prophylaxis / Assess for IRs
- Administer pegloticase infusion, per site guidelines

Visit 14 (18 weeks)

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Targeted Physical Exam and joint assessment
- Review concomitant medications, and record

- Assess any AEs, and record
- Gout Flare Assessment
- Laboratory Assessments
  - CBC with diff
  - sUA
  - Pregnancy test for premenopausal women
  - CMP
  - Pegloticase Antibody/Mechanistic Study
- Gout Flare Prophylaxis
- IR Prophylaxis /Assess for IRs
- Administer pegloticase infusion, per site guidelines

Visit 15 (20 weeks)

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Targeted Physical Exam and joint assessment
- Review concomitant medications, and record
- Assess any AEs, and record
- Gout Flare assessment
- PROs (PROMIS-29 & GIS instrument)
- Laboratory Assessments
  - CBC with diff
  - sUA
  - Pregnancy test for premenopausal women
  - CMP
- Gout Flare Prophylaxis
- IR Prophylaxis / Assess for IRs
- Administer pegloticase infusion, per site guidelines

Visit 16 (22 weeks)

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Targeted Physical Exam and joint assessment
- Review concomitant medications, and record
- Assess any AEs, and record
- Gout Flare assessment
- Laboratory Assessments
  - CBC with diff
  - sUA
  - Pregnancy test for premenopausal women
  - CMP
- Gout Flare Prophylaxis
- IR Prophylaxis /Assess for IRs
- Administer pegloticase infusion, per site guidelines.

Visit 17 (24 weeks)

Participants will complete a final physical exam and update their medical history since enrollment.

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Review concomitant medications, and record
- Assess any AEs, and record
- PROs (PROMIS-29 & GIS instrument)
- Physical exam
  - HEENT, and Neck
  - Cardiovascular
  - Respiratory
  - Gastrointestinal
  - Musculoskeletal
  - Neurologic
  - Integumentary
  - VS/Measurements
- Laboratory Assessments
  - CBC with diff
  - sUA
  - Pregnancy test for premenopausal women
  - CMP
  - Pegloticase Antibody/Mechanistic Study

Following completion of Visit 17 participants will continue for an additional 12 weeks without pegloticase infusions for anti-pegloticase antibody testing. In Phase 3, participants will continue with blood draws and banking of biospecimen every 4 weeks.

Reminder: if a participant is discontinued from the study, they will move into long-term follow-up and will be asked to complete visits 17, in addition to the three 1-month visits 18-20.

<u>Visit 18 (28 weeks)</u>
Participants will report 4 weeks following completion of Visit 17 for a blood draw and banking of biospecimen for anti-pegloticase antibody testing.

Assessments

- Adverse events
- Pegloticase Antibody/Mechanistic Study

<u>Visit 19 (32 weeks)</u>
Participants will report 4 weeks following completion of Visit 18 for a blood draw and banking of biospecimen for anti-pegloticase antibody testing.

Assessments

- Adverse events
- Pegloticase Antibody/Mechanistic Study

<u>Visit 20 (36 weeks-Final/visit)</u>
Participants will report 4 weeks following completion of Visit 19 for a blood draw and banking of biospecimen for anti-pegloticase antibody testing.

Assessments

- Adverse events

- Pegloticase Antibody/Mechanistic Study

Unscheduled Visit

An unscheduled Visit will be conducted in the event of a suspected AE thought to be serious.

- Obtain and record vital signs, including pulse rate, blood pressure, and body temperature
- Review concomitant medications, and record
- Assess any AEs, and record
- Physical exam includes, but is not limited to
  - HEENT, and Neck
  - Cardiovascular
  - Respiratory
  - Gastrointestinal
  - Musculoskeletal
  - Neurologic
  - Integumentary
  - VS/Measurements
- Laboratory Assessments
  - CBC with diff
  - IgG
  - sUA
  - CMP

  - Pegloticase Antibody/Mechanistic Study

Follow-up

We will follow each participant from screening for up to six months until completion of the full study (week 36). If the study drug is discontinued, unless the subject withdraws consent, the subject will be followed for the full study period and all data will be collected as scheduled.

9.1 EFFICACY ASSESSMENTS

We will assess the feasibility and preliminary efficacy of MMF's ability to safely attenuate immunogenicity conferred by pegloticase as determined by the proportion of participants randomized to peg + MMF achieving and maintaining an sUA ≤ to 6 mg/dL through 12 weeks (Visit 11), compared to concurrent controls (peg + PBO). After 12 weeks of co-administration of MMF or PBO, all participants will continue on pegloticase for an additional 12 weeks without combination therapy to determine the durability of immune modulation by assessing the absolute change in sUA from baseline to Week 24 (Visit 17), change in sUA from Week 12 (Visit 11) to Week 24 (Visit 17), and to determine the proportion of participants with sUA ≤ 6 mg/dL through Week 24 (Visit 17), and Week 12 (Visit 11) to Week 24 (Visit 17). Samples will be drawn for laboratory assessment at Visits 1-17 and at unscheduled visits. At visits 18-20 specimen samples will be collected for assessment of anti-pegloticase antibodies.

9.2 SAFETY AND OTHER ASSESSMENTS

Physical examination: A complete physical examination (e.g., height and weight, organ systems, motor or vision assessment, or other functional abilities) will be performed at Visit 1, Visit 11, and Visit 17. and targeted physical examination with joint assessment will be performed at Visit 3, 5, 7-10, 1217.

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

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

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.

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

population will be all participants who attend all study visits and complete the trial.

10.4 STATISTICAL ANALYSES

10.4.1 GENERAL APPROACH

RECIPE investigator Dr. Gary Cutter will oversee all data management and analysis for RECIPE DCC. The DCC is housed within the UAB School of Public Health. The DCC will ensure that the data collected and analyzed for this study are of the highest quality possible, and will be accomplished in part by having thorough edit checks as close to collection in time as possible, and updated as needed to guarantee high quality data through quality control and quality assurance. Edit checks will be reviewed by the statisticians, program manager, as well as other team members on an ongoing basis to evaluate whether any checks need to be added or any existing checks need to be modified. All data will be entered into the RECIPE electronic Data Entry System (eDES; Birmingham, AL) for seamless data management and auditing across the RECIPE sites (see MOOP Section 2.p). All analyses will be conducted using SAS (Cary, NC) Version 9.4 or higher or R-routines for specialty programs as needed.

One of the primary objectives of this feasibility pilot study is to determine if there is an overall reduction in immunogenicity leading to increased responders to pegloticase when MMF is co-administered in adults with chronic refractory gout. We have developed a decision table (see **Figure 4**) indicating when we will have sufficient evidence to move forward to a full scale clinical trial. **Figure 4** compares the success rates in the peg+MMF arm (N=24) versus peg+PBO (N=8). The area in green is the area that we will lead us to recommend continuing to test the treatment approach in a full scale study assuming safety. This green area represents the area that achieves a significant (2 tailed $p < 0.10$) Fisher's exact test that peg+MMF is better than pegloticase alone. The yellow area represents an achievement of a 2-tailed $p \leq 0.25$. If the results end up in the yellow or red areas, we will examine the Ab assays to determine if there is a clear significant difference in immune response. Based on these sample sizes, the mean difference in Ab titer level needs to be at least 1 standard deviation unit apart to achieve 73% power. Nevertheless, this would be a large difference for a clinical outcome variable, but for a marker such as Ab titers this is not unreasonable. Should the titer distributions not be consistent with normality assumptions, nonparametric analyses using a Wilcoxon test will be used, since the titer levels are already measured on a log scale precluding a simple transformation to achieve normality. Participants before the 12 weeks primary endpoint that do not tolerate MMF, or are lost to follow-up, withdraw, or are otherwise not evaluable will be counted *as failures* but not non-responders in sensitivity analyses. MMF efficacy will be examined by the proportion of responders and tested against the control group rate using Fisher's exact test. Success rates of the efficacy primary outcome will be determined using summary statistics and 95% confidence intervals. In the event of missing antibody data, imputations will be considered to assure data completeness for our analyses using PROC MI and PROC MIANALYZE procedures with 5 replicates per value. All analyses will be conducted using SAS (V9.4, Cary, North Carolina).

Figure 4. Decision to Pursue Future Clinical Trials (n = 32)

Success without MMF

Success with MMF

Successes	0	1	2	3	4	5	6	7	8
1	x	x	x	x	x	x	x	x	x
2	x	x	x	x	x	x	x	x	x
3	x	x	x	x	x	x	x	x	x
4	x	x	x	x	x	x	x	x	x
5	x	x	x	x	x	x	x	x	x
6	0.3	x	x	x	x	x	x	x	x
7	0.15	x	x	x	x	x	x	x	x
8	0.08	x	x	x	x	x	x	x	x
9	0.07	0.38	x	x	x	x	x	x	x
10	0.04	0.21	x	x	x	x	x	x	x
11	0.03	0.20	x	x	x	x	x	x	x
12	-*	0.10	0.41	x	x	x	x	x	x
13	-	0.05	0.23	x	x	x	x	x	x
14	-	0.04	0.22	x	x	x	x	x	x
15	-	0.04	0.11	0.25	x	x	x	x	x
16	-	-	0.10	0.22	x	x	x	x	x
17	-	-	0.04	0.12	0.4	x	x	x	x
18	-	-	0.03	0.09	0.22	x	x	x	x
19	-	-	-	0.07	0.18	x	x	x	x
20	-	-	-	0.02	0.15	0.33	x	x	x
21	-	-	-	0.01	0.05	0.15	x	x	x
22	-	-	-	-	0.02	0.09	0.25	x	x
23	-	-	-	-	-	0.04	0.15	x	x
24	-	-	-	-	-	0.01	0.06	0.25	x

* Dash indicates a highly significant 2 tailed p-value using Fishers exact test

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

MMF efficacy will be examined by the proportion of responders and tested against the control group rate using Fisher's exact test. Success rates of the efficacy primary outcome will be determined using summary statistics and 95% confidence intervals. As stated in section 10.4.1, should the success rates fall within the green area of **Figure 4** we will recommend testing in a larger study assuming safety and a demonstrated effect on Ab titers, our presumed intervening variable. We will examine failures and responders descriptively and via graphical methods.

10.4.3 ANALYSIS OF THE PRIMARY SAFETY AND SECONDARY ENDPOINT(S)

The ***primary safety aim*** will examine the number of patients experiencing the event and the total number of events, their severity and relatedness to study drug will be summarized and all AEs and SAEs reported. Ascertaining safety outcomes will be mostly descriptive and the confidence intervals will remain wide for the proportion of responders, based on n = 32, but strong evidence to proceed with a larger trial is necessary.

The ***secondary aims*** are to: 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 NIH supported Patient Reported Outcomes Measurement Information System (PROMIS)[57,58] and Gout Impact Scale (GIS)[59,60] instruments. For safety we will assess the incidence and types of adverse events / infusion reactions. The number of patients experiencing the event and the total number of events, their severity and relatedness to study drug will be summarized and all AEs and SAEs reported. Secondary endpoints including AEs across groups will be summarized using frequency and percentages. Continuous secondary outcome variables will be summarized using means with standard deviation (SD), and/or median and interquartile ranges (IQR) with 95% confidence intervals and compared by groups using t-tests or Wilcoxon tests as appropriate. Pegloticase Ab titers will be qualitatively analyzed for possible relationships with sUA lowering and the risk of IRs. Six month durability of response to MMF will be explored to assess if there is a threshold

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

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.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the NIAMS, IRBs, and/or FDA.

11.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy will be strictly held in trust by the participating investigators, their staff, and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the NIAMS, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigators, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or NIAMS requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the (DCC, based in the UAB Department of Biostatistics in the School of Public Health, directed by Dr. Gary Cutter (Co-Investigator). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be archived at UAB.

11.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the lab of John Mountz, MD, PhD at the University of Alabama at Birmingham. These samples could be used to for further research into the effects of MMF on pegloticase immunogenicity, its complications and other conditions for which individuals with gout are at increased risk, and to improve treatment. The Bridges Lab will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. When the study is completed, access to study data and/or samples will be reviewed and approved by the Coordinating Center at UAB, and provided through the Bridges Lab.

11.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor
Kenneth G. Saag, MD, MSc	Benjamin P. Butitta, MBA, CCRP
University of Alabama at Birmingham	University of Alabama at Birmingham
FOT 820, Birmingham AL 35294	Ryals School of Public Health
205-996-9784	225-603-5738
ksaag@uabmc.edu	bbutitta@uab.edu

11.1.6 SAFETY OVERSIGHT

In collaboration with NIAMS and KAI, we will convene a DSMB for additional monitoring of study procedures. The safety of the study participants is the highest priority for this project. The ability to make appropriate, sound scientific decisions regarding the outcome of each participant as early as possible is the top priority and as such, a process for the ongoing monitoring of results by independent scientists is important to maintain throughout the duration of the project. The DSMB will be comprised of 3 scientists who are independent of the study, the study investigators, and the University of Alabama at Birmingham and the University of Michigan for this clinical trial.

11.1.7 CLINICAL MONITORING

Benjamin Butitta, MBA, CCRP, a member of the DCC at UAB, will conduct clinical site monitoring. Clinical monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Sites will be monitored within at least 4-6 weeks of enrolling their second participant. Subsequent visits will take place every 6 months, or in the event there is an identified need for a visit. Independent audits will be conducted by the DCC to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

Case report forms and de-identified study source documents (including informed consent) for the first participant at each site will be submitted to the via email at recipe@uabmc.edu for review within 2 weeks of the baseline exam. Source documents will include: medical history, clinical notes, lab reports, informed consent process documentation, research lab worksheets, etc. Source documents will be checked against the eDES case report forms and the case report forms will be checked against the database tables. Printed laboratory reports and reports from the electronic medical record must include the date printed and signed by staff member printing the report. This will permit remote monitoring in a timely manner and can identify errors early in the data acquisition and entry process.

1. Monitoring visits will be conducted using the following guidelines:
   a. Sites will be notified at least 30 days prior to the site visit.
   b. 100% regulatory review, including informed consent review, will be conducted using a combination of files and onsite review.
   c. Ideally, at least one study participant record per activated clinical trial will be reviewed per site during a single visit
      - The data of a site's first enrollment will be 100% reviewed by the monitor.
      - At least one study participant case review will be conducted, with no upper limit; more cases can be added at the discretion of the DCC and monitor.
   d. The monitor will provide a preliminary report at the close of the monitoring visit.

e. The monitor (or designated representative) is responsible for writing a formal report no more than 10 business days following the visit. This will allow members of the DCC to review reports prior to formal submission to sites.
f. The monitoring visit report is sent initially to the DCC, and the study PI.
g. The study PI and study statistician will review the monitoring reports and make recommendations to the Site PI and monitor within 2 weeks of receipt.
h. It is the responsibility of the CCC to write a letter, and send it along with the report and any recommendations to the site PI of the institution being monitored, outlining any issues resulting from the monitoring visit. This will be done within one week of reviewing the monitoring report.
i. If the actions and responses are straightforward with no major concerns, the CCC will send a letter of compliance and recommendation of approval of the monitoring report and response(s).
j. The timeline for response will begin with a four week deadline. If further time is needed, the sanctioned institution may request (in writing) an extension and state the reason. If the institution in question is that of the study contact PI, the co-PI will be informed and issue the letter.

2. The Site PI responsibilities are:
   a. A reply to all issues addressed in monitoring report is due within 30 days of receipt of the monitoring review. This should be stipulated in the official letter. The letter should be sent via email notification.
   b. Serious issues may be referred to the DCC for further review. The DCC may decide to inform the DSMB.
   c. Once a site has responded to the requests in a timely manner, the DCC may either:
      - Send a formal closure letter stating that compliance has been met and close-out the monitoring review and follow-up.
      - Send a formal letter stating that compliance has not been met and the course of action that will follow; options may consist of any or all of the following:
        - Site visit and/or formal monitoring visit
        - Place the site on probation, with agreement of the CCC. The appropriate timeline to correct issues will be determined on a case-by-case basis depending upon the nature of the issue(s).
        - Require further training with a probationary period (to be determined)
        - Obtain recommendations from other groups, i.e., DSMB, sponsor, site IRBs and etc.
   d. Cases of severe non-compliance will be submitted to the CCC for recommendations that could result in:
      - Probation
      - Funding restrictions
      - A call to cease site enrollment
      - Report filed to the appropriate regulatory entities
      - Rejection of site status

   Once a site is placed on probation, reinstatement can occur only with a formal letter signed by the study PI. In cases where non-compliance pertains to the institution of the Study PI (K. Saag), then a letter signed by the co-PI (P. Khanna) would be sent.

   In addition, Drs. David Fox, MD (U. Michigan) and Angelo Gaffo, MD, MPH (UAB) will serve as medical monitors for the study. Drs. Fox and Gaffo will be consulted on an *ad hoc* to answer questions from clinical investigators at UAB, UM, and from participating clinical sites. Their primary responsibilities include (but are not limited to):

   - Providing medical leadership to sites by answering investigator questions about the protocol and the medical management of subject emergencies
   - Providing input on clinical development plans, protocol design, and risk assessments
   - Reviewing all study team deliverables, such as final narratives and clinical study reports
   - Reviewing and analyzing safety and efficacy trends

11.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures have been implemented beginning with the eDES data entry system and data QC checks that will be run on the database once enrollment begins. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

11.1.9 DATA HANDLING AND RECORD KEEPING

11.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All hardcopy source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the eCRF derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications) and clinical laboratory data will be entered into EDES, a 21 CFR Part 11-compliant data capture system provided by the Data Coordinating Center at the UAB School of Public Health. The eDES data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Printed laboratory reports and reports from the electronic medical record must include the date printed and signed by staff member printing the report.

As part of participating in a NIH-sponsored or NIH-affiliated study, each site will permit authorized representatives of the NIH, sponsor, and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity. Describe in this section who will have access to records.

11.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 7 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 7 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents will be retained for a longer period, however, if required by the IRB, FDA, or DSMB. No records will be destroyed without the written consent of the NIAMS.

11.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Operating Procedures (MOOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.
It will be the responsibility of the site investigator to use continuous vigilance to identify and report protocol deviations. Per the NIAMS reporting requirements, deviations/violations that impact participant safety will be reported to the NIAMS and the DSMB Safety Officer (through KAI) within 48 hours of the PI becoming aware of the event. Protocol

deviations/violations that occur but do not affect participant safety will be submitted with the routine DSMB meeting report.

11.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

Publication of results will be based on data from UAB and UM that has been analyzed as stipulated in the statistical analysis plan. We will not present data gathered from one site before the full publication, unless formally agreed to by all Investigators

By signing the protocol, the investigators will agree to keep all information in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents (protocols, Investigators' brochures, eCRFs and other material) will be stored appropriately to ensure their confidentiality. Individual patient data obtained during this study will be confidential and will not be disclosed to third parties with the following exceptions:

- When data are needed by the patient's personal physician or other medical personnel responsible for the patient's welfare. Prior written consent from the patient or legal guardian will first be obtained.
- For data inspection and verification by the IRB, or regulatory agency representatives.

Individual patient identity will not be divulged in any communication or publication.

In addition, this study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the Data Coordinating Center at UAB.

11.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Any actual or perceived conflicts of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed per the policies of the participating academic institutions. The respective academic institution conflict of interest review boards have established policies and procedures for all study group members to disclose all conflicts of interest and has mechanisms for the management of such conflicts.

11.2 ADDITIONAL CONSIDERATIONS

11.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

Ab	Antibody
AE	Adverse Event

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

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

		infusion. • Removal of CBC collection at run-in visit • Collection of banked specimen to measure adherence to MMF at all study visits during the dual therapy phase • Supply participants with a two-week supply of MMF/placebo and assess compliance at every infusion visit during the dual therapy phase • Addition of HDL/LDL collection time points • Addition of gene expression and epigenetics blood collection time points	at screening and before each infusion visit • Recommendation from the DSMB • By decreasing the number of pills given to participants, it will decrease participant burden due to high volume of pills and will increase compliance with study medication • Not usually included on CMP, need to specifically ask for lab values on lab order sheet • Tests added to measure the effect of urate-lowering therapy on the epigenome and gene expression
7.0	07/18/2018	• Addition of corticosteroids as second-tier rescue medication	• To improve patient quality and avoid dropouts, corticosteroids will be given if first-line medications (NSAIDS and colchicine) are ineffective
8.0	07/19/2018	• Addition of medical monitors	• Drs. David Fox and Angelo Gaffo have been added as medical monitors, and will assist/provide site investigators in answering clinical relevant questions
9.0	09/13/2018	• Deletion of LDL and HDL lab collection • Addition of sUA check at Visit 4	• Lab values are not necessary • To gain a better understanding of the sUA levels in between infusion 1 and 2.
10.0	12/04/2018	• Revision of follow-up visits post participant treatment failure/infusion reaction. Will conduct visit 17 (two weeks post treatment failure/infusion reaction) and visits 18-20 (once a month for three months)	• Participants who have experienced pegloticase treatment failure or otherwise discontinue pegloticase and are off study drug (MMF or placebo) require less regular safety evaluations. The half-life of MMF and pegloticase (the active medications) is about 17 hours and 10-12 days respectively. Adverse effects, which may be attributable to either drug, are time limited following treatment discontinuation. This revision will limit participant burden and encourage continuation in study.
11.0	1/10/2019	• Addition of a weight restriction of 160kg	• To minimize the likelihood of primary pegloticase treatment failures due to weight exceeding 160kg
12.0	1/13/2020	• Clarified recording of lab results and the process for signing off on labs • AE/SAE review	• Request from NIAMS/KAI • Request from NIAMS/KAI

12 REFERENCES

1. Sundy J. S., Becker M. A., Baraf H. S., Barkhuizen A., Moreland L. W., Huang W., Waltrip R. W., 2nd, Maroli A. N., Horowitz Z. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a phase II randomized study. Arthritis Rheum. 2008;58(9):2882-91. 10.1002/art.23810.
2. Administration Food and Drug.AAC Briefing Document Krystexxa (Pegloticase).2009.*http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM165714.pdf*. . March 23, 2016
3. Administration Food and Drug.KRYSTEXXA™ (pegloticase) for intravenous infusion BLA No. 125293 2009.*http://tinyurl.com/j293s5h*.
4. Baraf H. S., Matsumoto A. K., Maroli A. N., Waltrip R. W., 2nd**.** Resolution of gouty tophi after twelve weeks of pegloticase treatment. Arthritis Rheum. 2008;58(11):3632-4. 10.1002/art.23993.
5. Sundy J. S., Baraf H. S., Yood R. A., Edwards N. L., Gutierrez-Urena S. R., Treadwell E. L., Vazquez-Mellado J., White W. B., Lipsky P. E., Horowitz Z., Huang W., Maroli A. N., Waltrip R. W., 2nd, Hamburger S. A., Becker M. A. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA. 2011;306(7):711-20. 10.1001/jama.2011.1169.
6. Hershfield M. S., Ganson N. J., Kelly S. J., Scarlett E. L., Jaggers D. A., Sundy J. S. Induced and pre-existing anti-polyethylene glycol antibody in a trial of every 3-week dosing of pegloticase for refractory gout, including in organ transplant recipients. Arthritis Res Ther. 2014;16(2):R63. 10.1186/ar4500. 4060462
7. Singh J. A., Strand V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. Ann Rheum Dis. 2008;67(9):1310-6. 10.1136/ard.2007.081604.
8. Sattui S. E., Singh J. A., Gaffo A. L. Comorbidities in patients with crystal diseases and hyperuricemia. Rheum Dis Clin North Am. 2014;40(2):251-78. 10.1016/j.rdc.2014.01.005. Pmc4159668
9. Zhu Y., Pandya B. J., Choi H. K. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011;63(10):3136-41. 10.1002/art.30520.
10. Saag K. G., Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. Arthritis Res Ther. 2006;8 Suppl 1:S2. 10.1186/ar1907. Pmc3226107
11. Mikuls T. R., Farrar J. T., Bilker W. B., Fernandes S., Schumacher H. R., Jr., Saag K. G. Gout epidemiology: results from the UK General Practice Research Database, 1990-1999. Ann Rheum Dis. 2005;64(2):267-72. 10.1136/ard.2004.024091. Pmc1755343
12. Roddy Edward, Doherty Michael**.** Gout. Epidemiology of gout. Arthritis Research & Therapy. 2010;12(6):223-. 10.1186/ar3199.
13. Wertheimer Albert, Morlock Robert, Becker Michael A. A Revised Estimate of the Burden of Illness of Gout. Current Therapeutic Research. 2013;75:1-4. *http://dx.doi.org/10.1016/j.curtheres.2013.04.003*.
14. Brook R. A., Forsythe A., Smeeding J. E., Lawrence Edwards N. Chronic gout: epidemiology, disease progression, treatment and disease burden. Curr Med Res Opin. 2010;26(12):2813-21. 10.1185/03007995.2010.533647.
15. Khanna P., Khanna D., Storgard C., Baumgartner S., Morlock R. A world of hurt: failure to achieve treatment goals in patients with gout requires a paradigm shift. Postgrad Med. 2016;128(1):34-40. 10.1080/00325481.2016.1113840.
16. Schellekens H. Factors influencing the immunogenicity of therapeutic proteins. Nephrol Dial Transplant. 2005;20 Suppl 6:vi3-9. 10.1093/ndt/gfh1092.
17. Lipsky Peter E., Calabrese Leonard H., Kavanaugh Arthur, Sundy John S., Wright David, Wolfson Marsha, Becker Michael A. Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout. Arthritis Research & Therapy. 2014;16(2):R60-R. 10.1186/ar4497.
18. Baraf H. S., Yood R. A., Ottery F. D., Sundy J. S., Becker M. A. Infusion-related reactions with pegloticase, a recombinant uricase for the treatment of chronic gout refractory to conventional therapy. J Clin Rheumatol. 2014;20(8):427-32. 10.1097/rhu.0000000000000200. Pmc4280274
19. Baraf Herbert S. B., Becker Michael A., Gutierrez-Urena Sergio R., Treadwell Edward L., Vazquez-Mellado Janitzia, Rehrig Claudia D., Ottery Faith D., Sundy John S., Yood Robert A. Tophus burden reduction with pegloticase: results from phase 3 randomized trials and open-label extension in patients with chronic gout refractory to conventional therapy. Arthritis Research & Therapy. 2013;15(5):R137-R. 10.1186/ar4318.
20. Becker M. A., Schumacher H. R., Benjamin K. L., Gorevic P., Greenwald M., Fessel J., Edwards L., Kawata A. K., Frank L., Waltrip R., Maroli A., Huang B., Sundy J. S. Quality of life and disability in patients with treatment-failure gout. J Rheumatol. 2009;36(5):1041-8. 10.3899/jrheum.071229.
21. Hershfield M. S., Roberts L. J., 2nd, Ganson N. J., Kelly S. J., Santisteban I., Scarlett E., Jaggers D., Sundy J. S. Treating gout with pegloticase, a PEGylated urate oxidase, provides insight into the importance of uric acid as an antioxidant in vivo. Proc

Natl Acad Sci U S A. 2010;107(32):14351-6. 10.1073/pnas.1001072107. 2922538
22. Sundy J. S. Progress in the pharmacotherapy of gout. Curr Opin Rheumatol. 2010;22(2):188-93. 10.1097/BOR.0b013e3283369014.
23. Simkin P. A. Management of gout. Ann Intern Med. 1979;90(5):812-6.
24. Emmerson B. T. The management of gout. N Engl J Med. 1996;334(7):445-51. 10.1056/nejm199602153340707.
25. Schumacher H. R. Crystal-induced arthritis: an overview. Am J Med. 1996;100(2a):46s-52s.
26. Perez-Ruiz F., Calabozo M., Pijoan J. I., Herrero-Beites A. M., Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum. 2002;47(4):356-60. 10.1002/art.10511.
27. Wang K., Zhang H., Li Y., Wei Q., Li H., Yang Y., Lu Y. Efficacy of mycophenolate mofetil versus azathioprine after renal transplantation: a systematic review. Transplant Proc. 2004;36(7):2071-2. 10.1016/j.transproceed.2004.07.059.
28. Rathi M., Goyal A., Jaryal A., Sharma A., Gupta P. K., Ramachandran R., Kumar V., Kohli H. S., Sakhuja V., Jha V., Gupta K. L. Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis. Kidney Int. 2015. 10.1038/ki.2015.318.
29. Noureldeen T., Albekioni Z., Machado L., Muddana N., Marcus R. J., Hussain S. M., Sureshkumar K. K. Alemtuzumab induction and antibody-mediated rejection in kidney transplantation. Transplant Proc. 2014;46(10):3405-7. 10.1016/j.transproceed.2014.08.037.
30. Meriggioli M. N., Ciafaloni E., Al-Hayk K. A., Rowin J., Tucker-Lipscomb B., Massey J. M., Sanders D. B. Mycophenolate mofetil for myasthenia gravis: an analysis of efficacy, safety, and tolerability. Neurology. 2003;61(10):1438-40.
31. Krieckaert C. L., Bartelds G. M., Lems W. F., Wolbink G. J. The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review. Arthritis Res Ther. 2010;12(5):217. 10.1186/ar3147. 2991013
32. Maneiro J. R., Salgado E., Gomez-Reino J. J. Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated Inflammatory conditions: systematic review and meta-analysis. JAMA Intern Med. 2013;173(15):1416-28. 10.1001/jamainternmed.2013.7430.
33. Bartelds G. M., Krieckaert C. L., Nurmohamed M. T., van Schouwenburg P. A., Lems W. F., Twisk J. W., Dijkmans B. A., Aarden L., Wolbink G. J. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA. 2011;305(14):1460-8. 10.1001/jama.2011.406.
34. Dervieux T., Weinblatt M. E., Kivitz A., Kremer J. M. Methotrexate polyglutamation in relation to infliximab pharmacokinetics in rheumatoid arthritis. Ann Rheum Dis. 2013;72(6):908-10. 10.1136/annrheumdis-2012-202591.
35. Berhanu A. A., Krasnokutsky S., Keenan R. T., Pillinger M. H. Pegloticase failure and a possible solution: Immunosuppression to prevent intolerance and inefficacy in patients with gout. Semin Arthritis Rheum. 2016. 10.1016/j.semarthrit.2016.09.007.
36. Krieckaert C. L., Nurmohamed M. T., Wolbink G. J. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis. 2012;71(11):1914-5. 10.1136/annrheumdis-2012-201544.
37. Jani Meghna, Barton Anne, Warren Richard B., Griffiths Christopher E. M., Chinoy Hector**.** The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology (Oxford, England). 2014;53(2):213-22. 10.1093/rheumatology/ket260.
38. Rovin B. H., Furie R., Latinis K., Looney R. J., Fervenza F. C., Sanchez-Guerrero J., Maciuca R., Zhang D., Garg J. P., Brunetta P., Appel G. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012;64(4):1215-26. 10.1002/art.34359.
39. Ginzler E. M., Dooley M. A., Aranow C., Kim M. Y., Buyon J., Merrill J. T., Petri M., Gilkeson G. S., Wallace D. J., Weisman M. H., Appel G. B. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2005;353(21):2219-28. 10.1056/NEJMoa043731.
40. Kamanamool N., McEvoy M., Attia J., Ingsathit A., Ngamjanyaporn P., Thakkinstian A. Efficacy and adverse events of mycophenolate mofetil versus cyclophosphamide for induction therapy of lupus nephritis: systematic review and meta-analysis. Medicine (Baltimore). 2010;89(4):227-35. 10.1097/MD.0b013e3181e93d00.
41. Lee Y. H., Song G. G. Relative efficacy and safety of tacrolimus, mycophenolate mofetil, and cyclophosphamide as induction therapy for lupus nephritis: a Bayesian network meta-analysis of randomized controlled trials. Lupus. 2015;24(14):1520-8. 10.1177/0961203315595131.
42. Sollinger H. W. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. Transplantation. 1995;60(3):225-32.
43. Srinivas T. R., Kaplan B., Meier-Kriesche H. U. Mycophenolate mofetil in solid-organ transplantation. Expert Opin Pharmacother. 2003;4(12):2325-45. 10.1517/14656566.4.12.2325.
44. Magro-Checa C., Zirkzee E. J., Huizinga T. W., Steup-Beekman G. M. Management of Neuropsychiatric Systemic Lupus Erythematosus: Current Approaches and Future Perspectives. Drugs. 2016;76(4):459-83. 10.1007/s40265-015-0534-3. Pmc4791452

45. Prager David**.** Azathioprine and Allopurinol. Annals of Internal Medicine. 1974;80(3):427-. 10.7326/0003-4819-80-3-427_2.
46. Raman G. Venkat, Sharman V. L., Lee H. A. Azathioprine and allopurinol: a potentially dangerous combination. Journal of Internal Medicine. 1990;228(1):69-71. 10.1111/j.1365-2796.1990.tb00195.x.
47. Jacobs F., Mamzer-Bruneel M. F., Skhiri H., Thervet E., Legendre C., Kreis H. Safety of the mycophenolate mofetil-allopurinol combination in kidney transplant recipients with gout. Transplantation. 1997;64(7):1087-8.
48. Allison A. C., Eugui E. M. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology. 2000;47(2-3):85-118.
49. Mehling A., Grabbe S., Voskort M., Schwarz T., Luger T. A., Beissert S. Mycophenolate mofetil impairs the maturation and function of murine dendritic cells. J Immunol. 2000;165(5):2374-81.
50. Morgan S. L., Baggott J. E., Koopman W. J., Krumdieck C. L., Alarcón G. S. Folate supplementation and methotrexate. Annals of the Rheumatic Diseases. 1993;52(4):315-6.
51. Keenan R. T., O'Brien W. R., Lee K. H., Crittenden D. B., Fisher M. C., Goldfarb D. S., Krasnokutsky S., Oh C., Pillinger M. H. Prevalence of contraindications and prescription of pharmacologic therapies for gout. Am J Med. 2011;124(2):155-63. 10.1016/j.amjmed.2010.09.012.
52. Perez-Ruiz F., Nolla J. M. Influence of leflunomide on renal handling of urate and phosphate in patients with rheumatoid arthritis. J Clin Rheumatol. 2003;9(4):215-8. 10.1097/01.rhu.0000081470.31167.8b.
53. Lee J. J., Bykerk V. P., Dresser G. K., Boire G., Haraoui B., Hitchon C., Thorne C., Tin D., Jamal S., Keystone E. C., Pope J. E. Reduction in Serum Uric Acid May Be Related to Methotrexate Efficacy in Early Rheumatoid Arthritis: Data from the Canadian Early Arthritis Cohort (CATCH). Clin Med Insights Arthritis Musculoskelet Disord. 2016;9:37-43. 10.4137/cmamd.s38092. Pmc4821431
54. Ceschi A., Gregoriano C., Rauber-Luthy C., Kupferschmidt H., Banner N. R., Krahenbuhl S., Taegtmeyer A. B. Acute mycophenolate overdose: case series and systematic literature analysis. Expert Opin Drug Saf. 2014;13(5):525-34. 10.1517/14740338.2014.903032.
55. Hughes L. B., Morrison D., Kelley J. M., Padilla M. A., Vaughan L. K., Westfall A. O., Dwivedi H., Mikuls T. R., Holers V. M., Parrish L. A., Alarcon G. S., Conn D. L., Jonas B. L., Callahan L. F., Smith E. A., Gilkeson G. S., Howard G., Moreland L. W., Patterson N., Reich D., Bridges S. L., Jr. The HLA-DRB1 shared epitope is associated with susceptibility to rheumatoid arthritis in African Americans through European genetic admixture. Arthritis Rheum. 2008;58(2):349-58. 10.1002/art.23166. PMC3726059
56. Ostensen M., Khamashta M., Lockshin M., Parke A., Brucato A., Carp H., Doria A., Rai R., Meroni P., Cetin I., Derksen R., Branch W., Motta M., Gordon C., Ruiz-Irastorza G., Spinillo A., Friedman D., Cimaz R., Czeizel A., Piette J. C., Cervera R., Levy R. A., Clementi M., De Carolis S., Petri M., Shoenfeld Y., Faden D., Valesini G., Tincani A. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther. 2006;8(3):209. 10.1186/ar1957. PMC1526635
57. Wood R., Fermer S., Ramachandran S., Baumgartner S., Morlock R. Patients with Gout Treated with Conventional Urate-lowering Therapy: Association with Disease Control, Health-related Quality of Life, and Work Productivity. J Rheumatol. 2016. 10.3899/jrheum.151199.
58. Schalet B. D., Hays R. D., Jensen S. E., Beaumont J. L., Fries J. F., Cella D. Validity of PROMIS physical function measures in diverse clinical samples. J Clin Epidemiol. 2016. 10.1016/j.jclinepi.2015.08.039.
59. Sarkin A. J., Levack A. E., Shieh M. M., Kavanaugh A. F., Khanna D., Singh J. A., Terkeltaub R. A., Lee S. J., Hirsch J. D. Predictors of doctor-rated and patient-rated gout severity: gout impact scales improve assessment. J Eval Clin Pract. 2010;16(6):1244-7. 10.1111/j.1365-2753.2009.01303.x.
60. Wallace Beth, Khanna Dinesh, Aquino-Beaton Cleopatra, Singh Jasvinder A., Duffy Erin, Elashoff David, Khanna Puja P. Performance of Gout Impact Scale in a longitudinal observational study of patients with gout. Rheumatology. 2016. 10.1093/rheumatology/kew007.

UAB IRB Approved 16-Oct-2019 until 15-Oct-2020

TITLE:	REduCing Immunogenicity to PegloticasE (KRYSTEXXA® (RECIPE) Study
UAB IRB PROTOCOL NUMBER:	IRB-300000591
PRINCIPAL INVESTIGATOR:	Kenneth Saag, MD, MSc
HOSPITAL/INSTITUTION: **LOCATION:**	University of Alabama at Birmingham 115 Community Health Services Building Birmingham, AL 35294 (205)-934-9281
Funding Agency:	Horizon Pharma, PLC, and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

INTRODUCTION

You are being asked to participate in a clinical trial being conducted by Dr. Kenneth Saag. Dr. Saag thinks you may be a good candidate to participate in this study. You and your doctor have decided that you will begin treatment for your gout with a drug named KRYSTEXXA® (also known as pegloticase). The information in this form tells you about the clinical trial and what it means to participate in the study.

PURPOSE OF THE STUDY

You are being asked to take part in this clinical trial study because you have chronic gout and your signs and symptoms of gout are not controlled by your current medications. The purpose of this study is to figure out how to best use 8 mg of KRYSTEXXA ® in combination with the drug Mycophenolate Mofetil (MMF) also called CellCept® or mycophenolic acid (MPA) in patients 18 years of age and over for the treatment of chronic gout. KRYSTEXXA® has been approved by the US Food and Drug Administration (FDA) for the treatment of gout (caused by high uric acid). MMF is a US Food and Drug Administration (FDA) approved drug that affects the body's immune system and is used for many chronic diseases. Many gout patients that use KRYSTEXXA® develop antibodies and must stop using it. We are trying to determine if MMF can allow gout patients to use KRYSTEXXA® for a longer period of time.

DESCRIPTION OF THE STUDY,TESTS YOU WILL UNDERGO, AND OTHER THINGS YOU WILL BE ASKED TO DO DURING THE STUDY

You will be assigned by chance, similar to a flip of the coin, into one of two groups. Neither you nor Dr. Saag can choose the group you will be in and you will not know whether you are receiving Mycophenolate Mofetil or the inactive placebo (i.e., a sugar pill). One group will receive KRYSTEXXA® plus MMF therapy, and the other group will receive KRYSTEXXA® plus placebo therapy. The research will be conducted at the UAB Arthritis Clinical Intervention Program (ACIP) clinic.

Your participation in this study will be 40 weeks (see timeline), and will include 20 study related visits. At each of these visits blood collections and/or urine samples will be collected Study visits that include a KRYSTEXXA® infusion will last roughly 4 hours. All other study visits will last approximately 1 hour. The things you will be asked to do are described in detail later in the consent form.

The first visit will be for screening to determine if you can participate in the study and if you are free of any infections. You will be one of approximately 8 people at UAB to be asked to be in this study. Before you can start the study, the study doctor or study staff will talk to you about the study.

At this initial screening visit, you will undergo a blood draw, and physical examination where Dr. Saag and/or a member of the study team will ask you questions about your medical history. If you are unable to complete all screening tests, you will be scheduled to return to the study center within two days of Visit 1 (screening visit) to complete any outstanding screening tests. If you continue to qualify to participate in this study by meeting all study requirements, you will be scheduled to return to the study center two weeks after the screening visit.

During the study, it is possible that you may not meet certain study requirements at some study visits. If this happens the study doctor may discontinue your participation. If you are unable to continue in the study, you will stop receiving the study medication and your study doctor may advise you to start other treatments to control your gout. At that point, your participation in the study will end.

Blood Tests: Blood will be drawn 20 times during this study. Needle sticks are painful for a short period of time and sometimes will cause bruising at the site for a couple of days. You might feel dizzy or faint during a blood draw but this generally passes within a few minutes. Each time we draw blood, we will take about 1½ tablespoons of blood. We will do several tests to make sure it is safe to use the study medicine, and to look for any side effects of the study medicine to use the study medicines. This will include tests to check for infection, measure your kidney function, and to make sure you have enough of the enzyme glucose-6-phosphate dehydrogenase, or G6PD, which helps red blood cells (RBCs) function normally.

Urine Test and Collection: Women capable of becoming pregnant will have a serum pregnancy test to exclude women who are pregnant at the beginning of the study before enrollment and urine pregnancy tests before Visits 1-15 to make sure you do not become pregnant during the study period. The study doctor or study staff will tell you if the pregnancy test results are positive. The results of all pregnancy tests must be negative at each visit in order for you to participate in the study. Urine sample will be collected using a collection cup.

If you agree to participate in this research, the urine collected and/or blood drawn during your visits will be used for research purposes only. Your urine and blood samples will be labeled with a numerical code for analysis for this study in laboratories located at the University of Alabama at Birmingham. Any remaining samples may be used for further analysis of other related or unrelated research studies. However, you will have the option at the end of this consent form to not agree to the storage of your blood or urine samples for research purposes other than those specifically involved with this study.

VISIT 1

Before the study starts, you will be asked to sign this consent form and give your health history. The study doctor will perform procedures and tests to find out if you can be in the study. These tests include:

- Review inclusion and exclusion criteria to assess your eligibility for the study.
- Recording of your personal information, such as your name, age, race, etc.
- Recording of your medical and surgical history.
- Recording of all prior and current prescription medications, over the counter medications, vitamins and herbs. The study doctor may instruct you not to take certain medications within 48 hours of the next visit.
- A complete physical exam. You should ask the study doctor about what will happen during this exam.
- Collection of urine and blood samples (about 1½ tablespoons of blood) for clinical laboratory analysis and pregnancy screening for women of childbearing potential. The study doctor or study staff will tell you if the pregnancy test results are positive. The results of the pregnancy

test must be negative and you must be free of infection in order for you to be in the study.

VISIT 2

If you continue to qualify to participate in this study by meeting all study requirements, you will be scheduled to return to the study clinic within two weeks and will be given a two week supply of study medicine either MMF or placebo before beginning KRYSTEXXA® therapy. Neither the physician nor you will know if you are taking MMF or placebo. You will take one 500mg pill two times per day; once every morning at least 1 hour before breakfast and once every evening at least 1 hour before dinner. In addition, at Visit 2 we will collect blood to assess the medicine's safety and urine (women only) to test for pregnancy.

VISITS 3-20

The prescribing guidelines approved by the FDA for KRYSTEXXA® recommend that certain medicines should be given to help reduce your chance of having an allergic or other reaction to KRYSTEXXA®. These medicines will also be given before each treatment. In addition, all participants will receive medicine (colchicine 0.6mg/day or a non-steroidal anti-inflammatory) to reduce the risk of a gout flare or attack that you will continue for the duration of KRYSTEXXA® therapy. The study doctor or nurse will also perform procedures and tests to find out if you can be in the study. These tests include:

- Recording any updates of your medical and surgical history.
- Recording any updates to prescription medications, over the counter medications, vitamins and herbs.
- A targeted physical exam. You should ask the study doctor about what will happen during this exam.
- An assessment of your gout flare status and how your gout is affecting your activities to daily living
- Collection of urine and blood samples (about 1½ tablespoons of blood) for clinical laboratory analysis and pregnancy screening for women of childbearing potential. The study doctor or study staff will tell you if the pregnancy test results are positive. The results of the pregnancy test must be negative for you to be in the study.
- Recording any adverse events you may have experienced

Starting at Visit 3 you will be given a 4-week supply of MMF or placebo. You will take two 500 mg pills two times per day; once every morning at least 1 hour before breakfast and once every evening at least 1 hour before dinner. Neither the physician nor you will know if you are taking MMF or placebo. At visit 5 you will receive a new 4-week supply of supply of MMF or placebo. Following completion of visit 9 you will stop taking MMF or placebo, but will continue to receive KRYSTEXXA® every two weeks for the next 12 weeks. Upon completion of Visit 17 you will stop receiving KRYSTEXXA, and be asked to return monthly (every 4 weeks) for 3 months for a blood draw and banking of blood samples to check for other proteins in the blood (antibodies to KRYSTEXXA®).

You will be given a Medication Guide to read at each treatment visit and your doctor or study staff member will go over it with you before you receive your KRYSTEXXA® infusion.

You will be asked to stay for a post infusion observation (approximately 1 hour after completion of the KRYSTEXXA® infusion) in order to be observed for possible infusion-related reactions.

Also, at the first treatment visit, blood samples (up to 3 tablespoons) will be taken to check for other proteins in the blood (antibodies to KRYSTEXXA®). These samples taken before your first treatment will be compared to blood samples taken after you receive KRYSTEXXA®, we will compare the results if you ever have a serious allergic or other reaction when getting KRYSTEXXA®.

Blood samples (up to 3 tablespoons) are collected at each study visit and some of the blood samples collected may be used to help the study investigators determine study drug treatment effects, . These

samples may be stored for up to 7 years.

At every study visit, this blood sample is collected to check your serum urate (sUA) level will be collected. This check of sUA is part of the standard monitoring for any patient taking KRYSTEXXA®. Dr. Saag will also check whether your joints are tender or swollen. These exams will be repeated at the end of the study.

If you stop getting treatment before 12 weeks pass, you will be asked to stay in the study for follow-up. Follow-up consists of returning 8 weeks after the last infusion to collect formation on changes in your medical conditions and medications, and collect blood samples (up to 3 tablespoons) to check your body's reaction to KRYSTEXXA®.

RESEARCH PARTICIPANT RESPONSIBILITIES

As a participant in this research study, it is asked that you carefully follow the instructions of the study doctor and study staff. You will be asked to:

- Follow the instructions you are given.
- Read this Information and Consent Form and ask as many questions as needed.
- Provide the study doctor with a complete history of illnesses (and medications) you have had in the past.
- Tell the study doctor or study staff about any changes in your health or the way you feel.
- Tell the study doctor or study staff if you want to stop being in the study at any time.
- Provide the study doctor with the name, address, and phone number of your current regular doctor, and whether or not the study doctor can contact this doctor about your being in this study or to request your medical records.
- Keep to the schedule of visits and if there is a problem, call the study staff to reschedule.
- Take your study medication as directed. Do not abruptly stop taking study drug.
- Complete all tests and procedures to the best of your ability.
- Inform the study doctor or study staff of any medications you may have taken between visits.
- Ask questions during the study about anything you may be concerned about.
- Refrain from drinking excessive amounts of alcohol (no more than 2 drinks per day) and refrain from taking any illegal substances during this study.
- Refrain from exercise, smoking, drinking any caffeinated beverages, and eating or drinking grapefruit for at least two hours prior to each visit.
- Refrain from taking other medications for your gout (e.g. allopurinol) that the study doctor has asked you not to take while participating in this study.
- Fast overnight and the morning before coming to certain study visits if instructed to do so. Fasting means you are to have no food or drink except water for at least 8 hours before your study visit.
- Keep the provided study medication (mycophenolate mofetil or placebo) at room temperature and out of the reach of children or other adults. The provided study medication must be taken only by you, the person participating in the study.
- Do not donate blood while you are participating in the study and for up to one month after you have completed the study.
- You cannot participate in this study if you are pregnant.

POSSIBLE HAZARDS, RISKS, AND DISCOMFORTS OF PARTICIPATING IN THE STUDY

Participation in this study may involve some inconvenience, risks, or discomforts and it is very important that you tell your regular doctor or any other doctors or health care providers who treat you while you are in this study that you are in a research study. If you fail to do so, it could put you at significant risk. In addition, you will be assigned to a group by chance, which may prove to be less effective or to have more side effects than the other study group or alternatives.

Samples of blood for laboratory testing (up to 3 tablespoons) may be obtained from a vein (venous) in your arm at several study visits. The risks of drawing blood include temporary discomfort or slight bruising where the blood is drawn. Although rare, localized blood clotting and infections may occur.

Venous blood sampling will rarely cause bruising or a skin infection.

KRYSTEXXA®

Serious allergic infusion reactions may happen in some people who receive KRYSTEXXA®. KRYSTEXXA® should be given to you by a doctor or nurse in a healthcare setting where serious allergic reactions can be treated. In previous studies infusion reactions were reported in about a quarter (25%) of patients treated with KRYSTEXXA® usually within 2 hours after receiving KRYSTEXXA®. While most of these were considered mild or moderate, there is a chance that these reactions could be life threatening .You will be observed for any signs of a serious allergic reaction during and after your treatment with KRYSTEXXA®. Symptoms associated with infusion reactions that should be reported immediately to the study doctor or coordinator include:

- Wheezing,
- Shortness of breath,
- Cough,
- Chest discomfort
- Chest pain
- Trouble breathing
- Dizziness,
- Fainting,
- Fast or weak heartbeat or feeling nervous,
- Reddening of the face
- Rash, itching, hives, or feeling warm,
- Swelling of the throat or tongue, throat tightness, hoarse voice or trouble swallowing

Rates of infusion reactions may be significantly lessened by monitoring you for a rise in your serum urate level, which will be tested prior to each infusion, and not administering g pegloticase if this occurs.

Other symptoms occurring in at least 5% of patients treated with KRYSTEXXA® that may occur during the use of KRYSTEXXA® include gout flares also known as gout attacks (most common), dizziness, pain at injection site following infusion, vomiting, chills, higher blood pressure,, lower blood pressure, higher heart rate, and musculoskeletal discomfort..

If you experience any side effects from your gout therapy, report them as soon as possible to your doctor. If you experience any signs or symptoms of an allergic reaction, seek emergency treatment immediately, and notify your doctor.

Talk with your doctor about possible risks and side effects of taking KRYSTEXXA® and read the KRYSTEXXA® Medication Guide. Ask the study doctor if you have questions about these or other risks of taking KRYSTEXXA®.

There may also be risks associated with KRYSTEXXA® that are unknown at this time. You will be given more information if other risks are found.

MYCOPHENOLATE MOFETIL (MMF)

Let your study doctor know if you are allergic or have ever had any reactions to mycophenolate mofetil (MMF) or mycophenolic acid, the active drug form of mycophenolate mofetil. If you have, you should

not be enrolled in this study.

Mycophenolate mofetil is a marketed drug (CellCept®) approved for transplantation to prevent organ rejection. It works through suppressing your body's defense system. Mycophenolate mofetil, like other drugs that suppress your body's defense system, may decrease your body's ability to fight infection. In addition, it may make an existing infection harder to treat. You may also experience leukopenia (reduced white blood cell count) which may increase the risk of you getting an infection.

While taking MMF you may be at increased risk for bacterial, viral, fungal, and protozoal infections. Between one percent and ten percent (1%-10%) of patients who take MMF experience these infections. Discuss with the study doctor if you suspect that you have any current infections or have a past history of serious infections. You should also tell the study doctor if you have been in close contact with people who have been sick.

Mycophenolate mofetil may increase your risk of developing lymphoma (a type of cancer of white blood cells) and other malignancies, particularly of the skin (≤5%). To reduce your chances of skin cancer, you should wear protective clothing and using an effective sunscreen when in the sun.

In rare cases (< 1 in a thousand) mycophenolate mofetil may cause a serious infection of the brain. You should tell your doctor right away if you have any of the following symptoms:

- Weakness on one side of the body.
- You do not care about things that you usually care about (apathy).
- You are confused or have problems thinking.
- You cannot control your muscles.

About twenty percent (20%) of people who take mycophenolate mofetil experience gastrointestinal (gut) intolerance which may lead to nausea, diarrhea, and rarely gastrointestinal bleeding. These side effects typically subside over time. If you already have gastrointestinal problems, such as a peptic ulcer or inflammation of the digestive system, you should consult with your study doctor before taking mycophenolate mofetil.

There may also be risks associated with MMF that are unknown at this time. You will be given more information if other risks are found.

COLCHICINE

The most commonly reported side effects for the user of colchicine are diarrhea (23%) and sore throat (pharyngolaryngeal) pain (3%).Patients taking colchicine may experience gastrointestinal (digestive system) intolerance which may lead to nausea, persistent diarrhea, or rarely gastrointestinal bleeding (1%-10%). If you already have gastrointestinal problems, such as a peptic ulcer or inflammation of the digestive system, you should consult with your study doctor before taking colchicine.

Other side effects of taking colchicine include:

- Reduction in the number of white blood cells, leading to an increased risk of infection,
- Reduction in the number of red blood cells (anemia),
- Muscle weakness,
- Hair loss
- Skin rash
- Inflammation of a nerve
- Low sperm count

While taking colchicine you should avoid eating grapefruit and Seville oranges or drinking grapefruit juice or Seville orange juice. These can increase your chances of getting serious side

effects.

There may also be risks associated with colchicine that are unknown at this time. You will be given more information if other risks are found.

Finally, you may experience some anxiety while completing the brief questions about your gout history and gout flare status.

INFORMATION FOR WOMEN and MEN OF CHILDBEARING POTENTIAL

Women who are planning to become pregnant, pregnant, or breastfeeding may not participate in this study. The risks to pregnant women or an unborn baby when taking KRYSTEXXA® is not fully known. Mycophenolate mofetil use is associated with increased risks of pregnancy loss and congenital malformations.

For this reason, women must have a pregnancy test before the study starts and through Visit 15.. You must not become pregnant during this study. If you are a woman of childbearing potential, you 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 birth control (e.g. oral contraception, intrauterine device (IUD)), a double-barrier method (diaphragm with spermicide, condom with spermicide) or abstinence (not having sex).

If you think that you may have become pregnant during the study, you must contact the study doctor immediately and stop taking your study medication. If you become pregnant, you will be withdrawn from the study. Your study doctor may want to follow you and the outcome of your pregnancy.

Taking KRYSTEXXA® may involve unknown risks to a nursing infant. If you are breastfeeding, you cannot participate in the study.

Men who have not had a vasectomy are advised to either (a) abstain from reproductive sexual intercourse or (b) use a condom and contraceptive foam during intercourse. These precautions should be taken while on therapy and for at least one month after completing the study.

ALTERNATIVE

The alternative is to not participate in this study. If you decide to take part in this study, you are free to stop taking part in the study at any time. No matter what you decide to do, your decision to take part or not take part in this study will not affect your existing medical care.

SIGNIFICANT NEW FINDINGS

All new findings discovered during this research study that may reasonably influence your willingness to continue participation in this study will be provided to you when they become available.

BENEFITS OF THE STUDY

There may be no direct benefit to you. Your gout may improve while participating in this study, however this cannot be guaranteed.

You may also benefit by being followed for your gout and your general health status. The knowledge gained from this study could provide valuable information about gout and its treatments and, additionally, help other people with gout in the future. If successful, the study results may allow for safer, more effective treatment of gout.

COSTS

There is no cost for participating in this study. The study medications, KRYSTEXXA® and mycophenolate mofetil or placebo, will be provided to you at no charge. There will be no charge for the study visits or study procedures. The cost of any routine medical care needed during the study period will be billed to your insurance company in the usual manner. You or your insurance company will be

billed for any standard medical care during this study.

There will be no additional costs to you for procedures conducted specifically as part of this study, and not part of your regular gout treatment.

If you are in Medicare Advantage (Medicare managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional costs you could incur from participating in clinical trials.

PAYMENT FOR PARTICIPATION

You will be paid $25 by check for each study visit you complete. If you complete all (20) study visits you will receive up to a total of $500.00. If you are a UAB employee your payment(s) will be made by direct deposit.

CONFIDENTIALITY

Your personal information will be entered into a study database. Only study personnel will be able to enter and see information in this database. Research information that identifies you may be shared with the University of Alabama at Birmingham Institutional Review Board (IRB), Horizon Pharma, PLC, and others who are responsible for ensuring compliance with laws and regulations related to research, including the U.S. Food and Drug Administration (FDA), National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the Office for Humans Research Protections (OHRP). The information gathered during this study will be kept confidential to the extent permitted by law. The results of this study may be published in scientific journals or presented at medical meetings, but your identity will remain confidential.

Information relating to this study, including your name, medical record number, and date of birth may be shared with the billing offices of UAB and UAB Health System-affiliated entities so that claims may be appropriately submitted to the study sponsor or to the participant's insurance company for clinical services and procedures provided to participant during the course of this study.

COMPENSATION FOR INJURY

Horizon Pharma, PLC will pay for the cost of immediate medical care provided at UAB to treat an injury that has been determined by UAB to be a direct result of the tests or treatments that are done for this research. There are no plans for UAB or the Study Sponsors (Horizon Pharma, or the National Institute of Arthritis and Musculoskeletal and Skin Diseases) to pay for the costs of any additional care. There are no plans for UAB or the Study Sponsors to give you money for the injury.

STUDY RIGHTS AND STUDY WITHDRAWAL

Participation in this study is entirely voluntary. Your treatment and the attitude of your doctor toward you will not be affected should you decide not to take part in this study. Refusal to participate will not affect any benefits to which you are otherwise entitled. If you agree to participate, you may withdraw from the study at any time.

If you are a UAB student or employee, taking part in this research is not a part of your UAB class work or duties. You can refuse to enroll or withdraw after enrolling at any time before the study is over with no effect on your class standing, grades, or job at UAB. You will not be offered or receive any special consideration if you take part in this research.

You may refuse to participate or even withdraw once the study has started. In either case, you will not be penalized or lose any benefits to which you are otherwise entitled.

QUESTIONS

While you are participating in this study, if you have any questions or concerns, you should contact Dr. Saag or a member of his staff at 205-996-6086. After regular business hours (after 4pm and before

7am), please call 205-934-3411 and ask for Dr. Kenneth G. Saag to be paged.

You will be given a copy of this informed consent document and may ask for additional information at any time during the study from Dr. Saag or a member of his staff at 205-996-6086.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

A description of this clinical trial will be available on http://www.clinicaltrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

LEGAL RIGHTS

You are not waiving any of your legal rights by signing this consent form.

STORAGE OF SPECIMENS

As part of this study, we would like to store some of the blood and urine specimens collected from you for future gout research. The future research may be conducted by Dr. Kenneth Saag or by other researchers that obtain IRB approval for their research. The specimens will be labeled with a code that only Dr. Kenneth Saag or his staff can link back to you. Results of any future research will not be given to you or your doctor. The specimens obtained from you in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to you should this occur. As part of the analysis on your specimens, the investigators may do genetic testing. Genetic research is research that studies genes, including gene characteristic. Genetic research may include looking at information, such as biochemistry, gene sequences, genetic landmarks, individual and family medical histories, and reactions to medications and responses to treatment.

You do not have to agree to allow your blood and urine specimens to be stored in order to be part of this study.

You may request at any time that your research samples be removed from storage and not be used for future research. If you decide you want your samples removed, you may contact Dr. Kenneth Saag at the University of Alabama at Birmingham at 205-996-6086. Once the request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Initial your choice below:

_____ I agree to allow my samples to be kept and used for future research on gout.

_____ I do not agree to allow my samples to be kept and used for future research on gout.

SIGNATURES

Your signature below indicates that you agree to participate in this study. You will receive a copy of this signed informed consent.

_____

Printed Name of Participant

_____ _____

Signature of Participant Date

_____ _____

AUTHORIZATION FOR USE/DISCLOSURE OF PROTECTED HEALTH INFORMATION (PHI) FOR RESEARCH

Participant Name: _____
Research Protocol: _____

UAB IRB Protocol Number: IRB-300000591
Principal Investigator: Kenneth G. Saag, MD, MSc
Sponsor: Horizon Pharma, PLC and National Institute of Arthritis and Musculoskeletal and Skin Diseases

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your protected health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your protected health information may be used for the research.

Why do the researchers want my protected health information? The researchers want to use your protected health information as part of the research protocol listed above and as described to you in the informed consent.

What protected health information do the researchers want to use? All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills, and any other information related to or collected for use in the research protocol, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes.

Who will disclose, use and/or receive my protected health information? All Individuals/entities listed in the informed consent documents, including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees and agents, including any CRO; and any outside regulatory agencies, such as the Food and Drug Administration, providing oversight or performing other legal and/or regulatory functions for which access to participant information is required.

How will my protected health information be protected once it is given to others? Your protected health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel this Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the research protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the protected health information that was provided before you cancelled your authorization.

Can I see my protected health information? You have a right to request to see your protected health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____

or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____