IRB Conditions Satisfied at the Protocol Level
May 02, 2019

# CLINICAL STUDY PROTOCOL FOR KRYSTEXXA

**IND: 010122**

**Protocol Number: HZNP-KRY-202**

**Version 1.0**

## A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy and Safety Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled GOut Receiving KRYSTEXXA® (pegloticase) (MIRROR Randomized Controlled Trial [RCT])

## Short Title: MIRROR RCT

**Date: 17 April 2019**

**Sponsor:**
**Horizon Pharma Rheumatology LLC**
**150 S. Saunders Road**
**Lake Forest, IL 60045**

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**CONFIDENTIAL**

# PROTOCOL

## 1 TITLE PAGE

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|---|---|
| **Study Title:** | A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy and Safety Study of **M**ethotrexate to **I**ncrease **R**esponse **R**ates in Patients with Uncontrolled G**O**ut **R**eceiving KRYSTEXXA® (pegloticase) (MIRROR Randomized Controlled Trial [RCT]) |
| **Protocol Number:** | HZNP-KRY-202 |
| **Version:** | 1.0 |
| **Investigational Products:** | KRYSTEXXA (recombinant modified mammalian urate oxidase [uricase]); methotrexate (MTX) |
| **Indication:** | Chronic gout in adult patients refractory to conventional therapy |
| **Sponsor:** | Horizon Pharma Rheumatology LLC<br>150 S. Saunders Road<br>Lake Forest, IL 60045 |
| **Development Phase:** | 4 |
| **Sponsor's Responsible Medical Officer:** | Paul M. Peloso, MD<br>Vice President and Therapeutic Area Head, Rheumatology<br>Horizon Pharma USA, Inc.<br>150 S. Saunders Road<br>Lake Forest, IL 60045 |
| **Sponsor Signatory:** | Paul M. Peloso, MD<br>Vice President and Therapeutic Area Head, Rheumatology<br>Horizon Pharma USA, Inc.<br>150 S. Saunders Road<br>Lake Forest, IL 60045 |
| **Approval Date:** | 17 April 2019 |

**CONTACT IN THE EVENT OF AN EMERGENCY**

Any death, life-threatening event, or other serious adverse event experienced by a subject during the course of the study, whether or not judged drug-related, must be reported within 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF). If unable to access the eCRF, the event must be reported by submitting the completed Serious Adverse Event Form via email or fax to the contact numbers provided below.

Fax: 800-860-7836
Email: clinicalsafety@horizonpharma.com

# SPONSOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-202

Version: 1.0

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy and Safety Study of **M**ethotrexate to **I**ncrease **R**esponse **R**ates in Patients with Uncontrolled G**O**ut **R**eceiving KRYSTEXXA® (pegloticase) (MIRROR Randomized Controlled Trial [RCT])

Version Date: 17 April 2019

Approved by:

DocuSigned by:
Katie Obermeyer
Signer Name: Katie Obermeyer
Signing Reason: I approve this document
Signing Time: 4/17/2019 7:12:36 PM CDT
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Katie Obermeyer, MS
Associate Director, Biostatistics
Horizon Pharma USA, Inc.

Date

DocuSigned by:
Paul Peloso
Signer Name: Paul Peloso
Signing Reason: I approve this document
Signing Time: 4/17/2019 8:54:07 PM CDT
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Paul M. Peloso, MD
Vice President and Therapeutic Area Head, Rheumatology
Horizon Pharma USA, Inc.

Date

# PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-202

Version: 1.0

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy and Safety Study of **M**ethotrexate to **I**ncrease **R**esponse **R**ates in Patients with Uncontrolled G**O**ut **R**eceiving KRYSTEXXA® (pegloticase) (MIRROR Randomized Controlled Trial [RCT])

Version Date: 17 April 2019

I agree to conduct the study according to the protocol named above. I fully understand that any changes instituted by the Principal Investigator without previous discussion with the Sponsor constitute a violation of the protocol, unless necessary to eliminate an immediate hazard to the safety or well-being of a subject.

I acknowledge that I have read and understand the protocol named above and agree to carry out all of its terms in accordance with applicable regulations and laws.

I assure that the study drug supplied by the Sponsor will be used only as described in the protocol named above.

Signature:

_____ _____

Name Date
Study Center
Address
City State Country

# 2 SYNOPSIS

| **Protocol Title**: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy and Safety Study of **M**ethotrexate to **I**ncrease **R**esponse **R**ates in Patients with Uncontrolled G**O**ut **R**eceiving KRYSTEXXA® (pegloticase) (MIRROR Randomized Controlled Trial [RCT]) | |
|---|---|
| **Protocol Number:** HZNP-KRY-202 | **Phase:** 4 |
| **Protocol Version:** 1.0 | |
| **Test Drugs:** pegloticase; methotrexate (MTX), placebo for MTX | **Indication**: Chronic gout in adult patients refractory to conventional therapy |
| **Number and Country of Study Sites:** Approximately 65 study centers in the United States | |

**Objectives:**
The overall objective of this study is to assess the potential for pegloticase with MTX to increase the response rate seen with pegloticase alone, and to characterize the safety, tolerability and pharmacokinetics (PK) of the concomitant use of pegloticase with MTX, by comparing pegloticase co-administered with MTX to pegloticase co-administered with placebo for MTX in adults with uncontrolled gout.

Primary Objective

The primary objective is to evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the response rate during Month 6 (Weeks 20, 21, 22, 23 and 24), as measured by the sustained normalization of serum uric acid (sUA) to <6 mg/dL for at least 80% of the time during Month 6.

Secondary Objectives (analyzed sequentially)

1. Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the response rate during Month 9 (Weeks 32, 34, and 36), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 9.
2. Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the response rate during Month 12 (Weeks 48, 50, and 52), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 12.
3. Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the complete resolution of ≥ 1 tophi (using digital photography) at Week 52 in subjects with tophi at baseline.

Exploratory Objectives

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in urate deposition volume and bone erosions due to gout to Weeks 14, 24, and 52 based on dual-energy computed tomography (DECT) of the hands and feet.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in bone erosions due to gout to Weeks 24 and 52 based on X-rays of the hands and feet.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the complete resolution of ≥ 1 tophi (using digital photography) at Weeks 24 and 36 in subjects with tophi at baseline.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in tophus size (long axis measured using digital photography) to Weeks 14, 24, 36 and 52 in subjects with tophus present at baseline.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the response rate during Month 3 (Weeks 10, 12 and 14), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 3.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the overall response rate, as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 3 (Weeks 10, 12, and 14) and Month 6 (Weeks 20, 21, 22, 23, and 24) combined.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on reducing sUA to < 5 mg/dL for at least 80% of the time during Months 3, 6, 9 and 12, individually.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in sUA at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the time to first sUA > 6 mg/dL.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the time to two consecutive sUA > 6 mg/dL (sUA stopping rule).
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the percentage of non-hyperuricemic (sUA < 6 mg/dL) time during Months 3, 6, 9 and 12.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in HAQ Pain Score at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in HAQ Health Score at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase and MTX vs. pegloticase and placebo for MTX on the mean change from baseline in HAQ-DI Score at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in tender joint count (68-point scale) at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in swollen joint count (66-point scale) at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in number of tender or swollen joints at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in physician global assessment of gout at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the proportion of subjects whose treatment goals are met at Weeks 24 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) to each visit.
- Assess the PK of pegloticase.
- Assess the incidence of anti-PEG and anti-Uricase IgG antibodies.

Safety and Tolerability Objectives

- AE/SAE profile overall for pegloticase and the combination of pegloticase and MTX
  - Incidence of AESI: IRs, anaphylaxis, gout flares, cardiovascular events
- Laboratory tests
- Vital signs and physical examination

**Study Design**

This study is a Phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of pegloticase with MTX vs. pegloticase with placebo for MTX in adult subjects with uncontrolled gout.

The study design will include: 1) a Screening Period (screening should be completed within 4 weeks prior to Week -6); 2) a 2-week MTX Tolerability Assessment Period consisting of 2 weeks oral MTX for all subjects; 3) a Run-In Period consisting of randomization followed by 4 weeks of blinded oral MTX or placebo for MTX; 4) a

52-week Pegloticase + IMM Period; 5) a Safety Follow-up (Phone/Email/Site Visit) and 6) a 3 and 6 month Post Treatment Follow-up.

All subjects who meet eligibility criteria at Screening will begin 15 mg MTX orally weekly at the Week -6 visit. Subjects will also take folic acid 1 mg orally every day beginning during the MTX Tolerability Assessment Period (Week -6 to Week -4) and continuing until prior to the Week 52 Visit.

Subjects must be able to tolerate the weekly dose of MTX 15 mg for 2 weeks to be eligible to be randomized at Week -4. Subjects who are unable to tolerate the 15 mg dose of MTX during the 2 weeks preceding the Week -4 visit will be considered screen failures.

Subjects who tolerate the weekly 15 mg MTX dose during the 2 weeks preceding Week -4 Visit and continue to meet eligibility criteria will be randomized at the Week -4 Visit in a 2:1 ratio (stratified by presence of tophi) to receive either blinded oral 15 mg MTX or blinded oral placebo for MTX. Subjects will continue to take the blinded MTX or placebo for MTX from Week -4 to Day 1 (the Run-in period) at the 15 mg MTX or placebo for MTX dose. If a subject does not tolerate the 15 mg MTX or placebo for MTX dose after randomization at the Week -4 Visit and prior to Day 1, the MTX or placebo for MTX may be dose-reduced or discontinued based on pre-specified criteria and after discussion with the Sponsor medical monitor. The subject will be allowed to remain in the study. After Day 1, MTX or placebo for MTX may be re-initiated. The subject will be re-initiated to the same treatment they were randomized to at Week -4. The re-initiated MTX or placebo for MTX will remain blinded.

All subjects who complete the Run-In Period will receive the first pegloticase infusion on Day 1. All subsequent doses and study visits will be scheduled based on the Day 1 visit date.

It is required that before a subject begins the pegloticase + IMM Period, he or she has been taking at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤10 mg/day) for ≥1 week before the first dose of pegloticase and continues flare prophylaxis per American College of Rheumatology guidelines [Khanna D et al. 2012] for the greater of 1) 6 months, 2) 3 months after achieving target serum urate (sUA < 6 mg/dL) for patients with no tophi detected on physical exam, or 3) 6 months after achieving target serum urate (sUA < 5 mg/dL) for patients with one or more tophi detected on initial physical exam that have since resolved. For IR prophylaxis, fexofenadine (180 mg orally) will be taken the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, immediately prior to each infusion.

During the Pegloticase + IMM Period, pegloticase 8 mg will be administered intravenously (IV) every 2 weeks from Day 1 through the Week 50 Visit for a total of 26 infusions; pegloticase will be administered after all pre-dose study visit assessments have been completed at each visit. The date and start and stop time of infusion will be recorded. Serum uric acid stopping rules will be applied: subjects with sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue treatment, complete the End of Pegloticase Infusion Visit procedures within 2 weeks, and continue the subject visits according to the protocol (without treatment).

During the Pegloticase + IMM Period, subjects will be instructed to take MTX or placebo for MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase infusion and one additional weekly dose after the last infusion for subjects who have not stopped pegloticase due to sUA stopping rules; however, if a subject does not do so, MTX or placebo for MTX must be taken ≥60 minutes prior to each pegloticase infusion.

After Day 1, if a subject becomes unable to tolerate MTX or placebo for MTX, the MTX or placebo for MTX dose may be reduced and/or discontinued based on pre-defined criteria, and the subject may remain in the study.

The Investigator will review the clinical status and individual subject treatment goals at Screening, Week 24, the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of Study/Early Termination Visit.

After the Week 52 Visit (or End of Pegloticase Infusion Visit [if applicable]), subjects should resume regular care for gout per the judgment of the treating physician, including resumption of ULT upon pegloticase

discontinuation, if appropriate. Subjects will have a 3 and 6 Month Follow-up visit to assess clinical status, including sUA levels.

Samples for measurement of sUA levels, PK analysis of pegloticase, pegloticase immunogenicity and MTX Polyglutamate analysis will be collected at visits indicated in the Schedule of Assessments (Section 2.1).

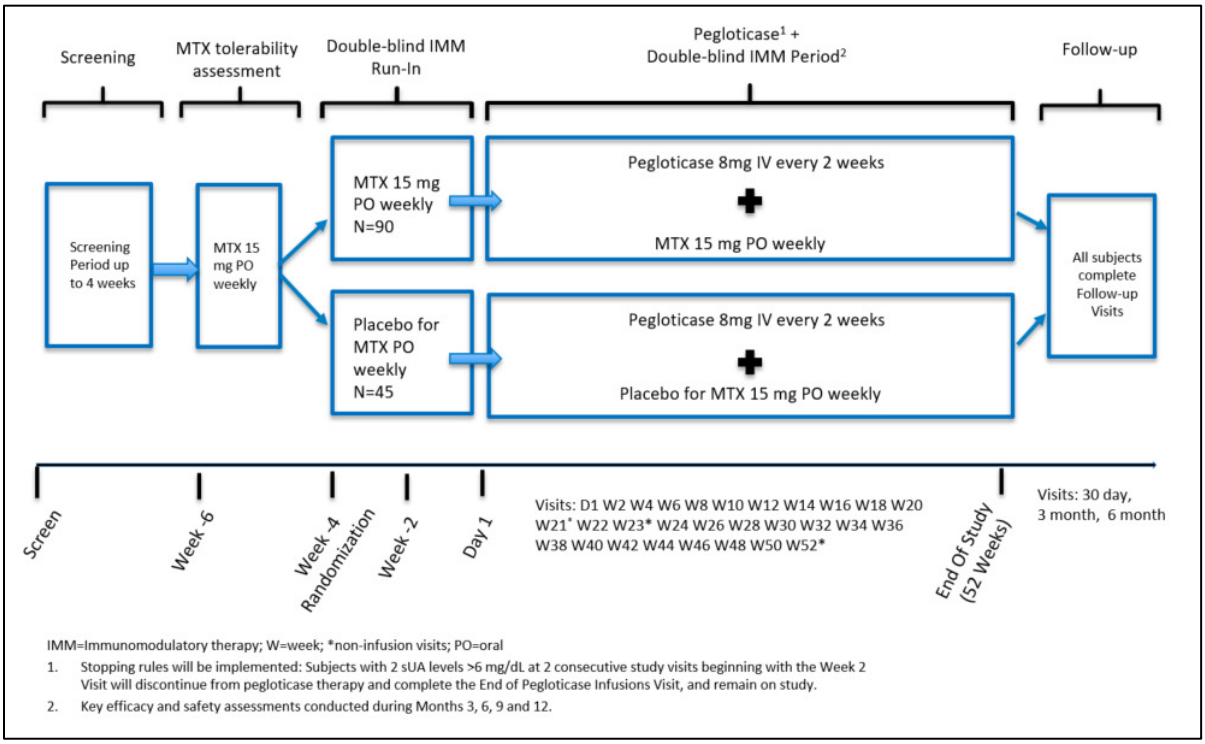
Safety assessments, including monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations, and monitoring of hematology and blood chemistry, will be performed.

An external Data Monitoring Committee (DMC) will be convened to review data for safety and efficacy with timing and criteria outlined in the DMC Charter, with the possibility of DMC recommendation on study conduct modification per criteria also to be outlined in the Charter.

An independent external adjudication committee will review reported events of infusion reactions, cardiovascular events and anaphylaxis.

An overview of the study design is presented in the schematic below, and details of study activities are provided in Section 2.1.

**Study Design (continued):**




IMM=Immunomodulatory therapy; W=week; *non-infusion visits; PO=oral

1. Stopping rules will be implemented: Subjects with 2 sUA levels >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue from pegloticase therapy and complete the End of Pegloticase Infusions Visit, and remain on study.
2. Key efficacy and safety assessments conducted during Months 3, 6, 9 and 12.

**Subject Population:**

Subjects eligible for this study will have sUA ≥7 mg/dL and gout refractory to conventional therapy characterized by failure to normalize serum uric acid despite conventional therapy or contraindication to conventional therapy, and ongoing symptoms of gout including one of the following: visible tophi, recurrent gout flares, or chronic gouty arthropathy.

**Inclusion Criteria:**

Eligible subjects must meet/provide **all** of the following criteria:

1. Willing and able to give informed consent.
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.
3. Adult men or women ≥18 years of age.
4. Uncontrolled gout, defined as meeting the following criteria:
   - Hyperuricemia during the screening period defined as sUA ≥7 mg/dL, and;
   - Failure to maintain normalization of sUA with xanthine oxidase inhibitors at the maximum medically appropriate dose, or with a contraindication to xanthine oxidase inhibitor therapy based on medical record review or subject interview, and;
   - Symptoms of gout including at least 1 of the following:
     - Presence of at least one tophus
     - Recurrent flares defined as 2 or more flares in the past 12 months prior to screening
     - Presence of chronic gouty arthritis
5. Willing to discontinue any oral urate lowering therapy for at least 7 days prior to MTX dosing at Week -6 and remain off when receiving pegloticase infusions.
6. Women of childbearing potential (including those with an onset of menopause <2 years prior to screening, non-therapy-induced amenorrhea for <12 months prior to screening, or not surgically sterile [absence of ovaries and/or uterus]) must have negative serum/urine pregnancy tests during Screening and Week -6; subjects must agree to use 2 reliable forms of contraception during the study, one of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started ≥1 full cycle prior to Week -6 (start of MTX) and continue for 30 days after the last dose of pegloticase, or at least one ovulatory cycle after the last dose of MTX or placebo for MTX (whichever is the longest duration after the last dose of pegloticase or MTX or placebo for MTX). Highly effective contraceptive methods (with a failure rate <1% per year), when used consistently and correctly, include implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or vasectomized partner.
7. Men who are not vasectomized must agree to use appropriate contraception so as to not impregnate a female partner of reproductive potential during the study, beginning with the initiation of MTX at Week -6 and continuing and for at least 3 months after the last dose of MTX or placebo for MTX.
8. Able to tolerate MTX 15 mg orally for 2 weeks (Week -6 through Week -4) prior to randomization.

**Exclusion Criteria:**

Subjects will be ineligible for study participation if they meet **any** of the following criteria:

1. Weight >160 kg (352 pounds) at Screening.
2. Any serious acute bacterial infection, unless treated and completely resolved with antibiotics at least 2 weeks prior to the Week -6 Visit.
3. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis.
4. Current or chronic treatment with systemic immunosuppressive agents such as MTX, azathioprine, or mycophenolate mofetil; prednisone ≥10 mg/day or equivalent dose of other corticosteroid on a chronic basis (3 months or longer) would also meet exclusion criteria.
5. History of any transplant surgery requiring maintenance immunosuppressive therapy.
6. Known history of hepatitis B virus surface antigen positivity or hepatitis B DNA positivity.
7. Known history of hepatitis C virus RNA positivity.
8. Known history of Human Immunodeficiency Virus (HIV) positivity.
9. Glucose-6-phosphate dehydrogenase deficiency (tested at the Screening Visit).
10. Chronic renal impairment defined as estimated glomerular filtration rate (eGFR) <40 mL/min/1.73 $m^2$ or currently on dialysis.
11. Non-compensated congestive heart failure or hospitalization for congestive heart failure within 3 months of the Screening Visit, uncontrolled arrhythmia, treatment for acute coronary syndrome (myocardial infarction or unstable angina), or uncontrolled blood pressure (>160/100 mmHg) prior to Randomization at Week -4.
12. Pregnant, planning to become pregnant, breastfeeding, planning to impregnate female partner, or not on an effective form of birth control, as determined by the Investigator.
13. Prior treatment with pegloticase, another recombinant uricase (rasburicase), or concomitant therapy with a polyethylene glycol-conjugated drug.
14. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product.
15. Contraindication to MTX treatment or MTX treatment considered inappropriate.
16. Known intolerance to MTX.
17. Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to MTX administration at Week -6 or plans to take an investigational drug during the study.
18. Liver transaminase levels (AST or ALT) > upper limit of normal (ULN) or albumin < the lower limit of normal (LLN) at the Screening Visit.
19. Chronic liver disease.
20. White blood cell count < 4,000/ul, hematocrit < 32 percent, or platelet count <75,000/ul.
21. Currently receiving systemic or radiologic treatment for ongoing cancer.
22. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix.
23. Diagnosis of osteomyelitis.
24. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
25. Unsuitable candidate for the study, based on the opinion of the Investigator (e.g., cognitive impairment), such that participation might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements or complete the study.
26. Alcohol use in excess of 3 alcoholic beverages per week.
27. A known intolerance to at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤10 mg/day).
28. Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest X-ray may be performed during Screening.

**Dose Regimen/Route of Administration:**

**MTX or placebo for MTX:**

During the MTX Tolerability Assessment Period (Week -6 until the Week -4 visit), all subjects will take MTX 15 mg orally weekly.

At the Week -4 visit, subjects who tolerated MTX will be randomized to receive MTX 15 mg or placebo for MTX orally weekly. Subjects will be blinded to MTX or placebo for MTX beginning at Week -4 through the remainder of the study. Subjects will continue to take the blinded MTX or placebo for MTX during the Run-in Period (from Week -4 to Day 1) at the 15 mg MTX dose or placebo for MTX dose. If a subject does not tolerate the 15 mg MTX or placebo for MTX dose after randomization at the Week -4 Visit and prior to Day 1, the MTX or placebo for MTX may be dose-reduced or discontinued based on pre-specified criteria and after discussion with the Sponsor medical monitor. The subject will be allowed to remain in the study. After Day 1, MTX or placebo for MTX may be re-initiated. The subject will be re-initiated to the same treatment they were randomized to at Week -4. The re-initiated MTX or placebo for MTX will remain blinded. During the Run-in Period, if a dose is missed, it should be taken as soon as it is remembered. If it is within 48 hours of the next scheduled dose, the subject will be instructed to skip the missed dose and resume at the next regularly scheduled time; thus, subjects will be instructed not to double a dose to make up for a missed dose if within 48 hours of the next dose.

During the Pegloticase + IMM Period, subjects will be instructed to take MTX or placebo for MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase infusion and one additional weekly dose after the last infusion for subjects who have not stopped pegloticase due to sUA stopping rules; however, if a subject does not do so, MTX or placebo for MTX must be taken ≥60 minutes prior to each pegloticase infusion. If a subject becomes unable to tolerate the MTX or placebo for MTX during the Pegloticase + IMM Period, the dosage may be decreased.

Subjects will also take folic acid 1 mg orally every day beginning during the MTX Tolerability assessment (Week -6 to Week -4) and continuing until prior to the Week 52 Visit.

**Pegloticase:**

All subjects who meet the inclusion/exclusion criteria and complete the Run-In Period will receive pegloticase at a dose of 8 mg administered IV every 2 weeks for a total of 26 infusions from Day 1 through the Week 50 Visit, inclusive (Pegloticase + IMM Period). The date and start and stop time of infusion will be recorded. Subjects will not be fasting on the day of infusion and will be encouraged to have a snack or normal meal before or after the infusion. All subjects will receive standardized prophylactic treatment to reduce the risk of acute gout flares, beginning ≥1 week before the first dose of pegloticase and continues flare prophylaxis per American College of Rheumatology guidelines [Khanna D et al. 2012] for the greater of 1) 6 months, 2) 3 months after achieving target serum urate (sUA < 6 mg/dL) for patients with no tophi detected on physical exam, or 3) 6 months after achieving target serum urate (sUA < 5 mg/dL) for patients with one or more tophi detected on initial physical exam that have since resolved. Standardized IR prophylaxis consisting of pre-treatment with antihistamines, acetaminophen and corticosteroids will accompany each infusion.

**Dosage Form and Strength Formulation (Pegloticase, MTX and placebo for MTX):**

Pegloticase (KRYSTEXXA) is commercially available in the United States and will be packaged in sterile, single-use 2-mL glass vials with a Teflon®-coated (latex-free) rubber injection stopper to deliver pegloticase as 8 mg of uricase protein in 1 mL volume. Pegloticase will be administered as an admixture of 8 mg in 250 mL of 0.45% or 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump. Pegloticase will not be administered as an IV push or bolus.

MTX 2.5 mg tablets for oral administration during the MTX Tolerability Assessment Period (Week -6 through Week -4) will be provided to subjects as a commercially available generic.

MTX 2.5 mg tablets for oral administration during the Run-In Period (Week -4 through Day 1) and the Pegloticase + IMM Period (Day 1 through Week 52) will be provided to subjects as a methotrexate 2.5 mg tablet over-encapsulated in a size zero Swedish Orange capsule.

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|---|
| Placebo for methotrexate 2.5 mg for oral administration during the Run-In Period (Week -4 through Day 1) and the Pegloticase + IMM Period (Day 1 through Week 52) will be provided as a size zero Swedish Orange capsule with Avicel® filling. |
| **Duration of Treatment and Follow-up:**<br>**Screening:** Completed within 4 weeks prior to the Week -6 visit<br>**MTX Tolerability Assessment Period (Week -6 through Week -4):** 2 weeks of oral MTX for all subjects<br>**Run-in Period (Week -4 through Day 1):** Randomization followed by 4 weeks of blinded oral MTX or placebo for MTX.<br>**Pegloticase + IMM Period (Day 1 through Week 52)**: MTX or placebo for MTX dosed weekly and 50 weeks of pegloticase infusion visits every 2 weeks; Non-infusion visits at Weeks 21, 23 and 52.<br>**End of Pegloticase Infusions Visit (if applicable)**: If the subject discontinues pegloticase treatment prior to infusion Week 50, such as due to the sUA stopping rules, the subject will complete this visit within approximately 2 weeks of the last infusion. Subjects will continue study.<br>**End of Study/Early Termination Visit:** Week 52 or earlier if the subject withdraws consent to participate in the study.<br>**Safety Follow-up Phone/Email Visit or Visit:**<br>All subjects will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of pegloticase to assess if any SAE's have occurred. Subjects who receive at least one dose of MTX or placebo for MTX and are females of childbearing potential, will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of MTX or placebo for MTX to verify at least one ovulatory cycle has occurred after the last dose of MTX or placebo for MTX. If the subject has not ovulated, a urine pregnancy test will be performed. Subjects who receive at least one dose of MTX and are non-vasectomized males, a phone/e-mail inquiry will be conducted 3 months after MTX discontinuation regarding partner pregnancy (inquiry can occur during the 3 month Post Treatment Follow-up).<br>**3 and 6 Month Post Treatment Follow-up:**<br>All subjects will be followed for a minimum of 6 months following the last infusion, with follow-up after Week 52 as warranted. |
| **Criteria for Evaluation:**<br>Efficacy will be assessed by sUA levels, tophus resolution, tophus size, tender and swollen joint counts, physician global assessment of gout, and DECT and X-ray of hands and feet.<br>Quality of life will be assessed using the HAQ.<br>The PK of pegloticase will be assessed prior to and after the pegloticase infusion at specified time points.<br>Pegloticase immunogenicity will be assessed by the incidence of anti-PEG and anti-uricase IgG antibodies prior to the pegloticase infusion at specified time points.<br>Safety assessments will include monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations, and monitoring of hematology and blood chemistry. |
| **Stopping Rules:**<br>**Individual Subject Stopping Rule:**<br>Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study. |

**Statistical Analyses:**

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of Month 6 (Weeks 20, 21, 22, 23 and 24) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.

Secondary Efficacy Endpoints

The secondary endpoints will be analyzed sequentially:

1. The proportion of Month 9 (Weeks 32, 34, and 36) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 9.
2. The proportion of Month 12 (Weeks 48, 50, and 52) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 12.
3. The proportion of subjects with complete resolution of ≥ 1 tophi (using digital photography) at Week 52 in subjects with tophi at baseline.

Exploratory Efficacy Endpoints

- The mean change from baseline to Weeks 14, 24 and 52 in urate volume and bone erosions due to gout based on DECT of the hands and feet.
- The mean change from baseline to Weeks 24 and 52 in bone erosions due to gout based on X-rays of the hands and feet.
- The proportion of subjects with complete resolution of ≥ 1 tophi (using digital photography) at Weeks 24 and 36 in subjects with tophi at baseline.
- The mean change from baseline in tophus size (long axis measured using digital photography) to Weeks 14, 24, 36 and 52 in subjects with tophus present at baseline.
- The proportion of Month 3 (Weeks 10, 12, and 14) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 3.
- The proportion of overall responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 3 (Weeks 10, 12, and 14) and Month 6 (Weeks 20, 21, 22, 23 and 24) combined.
- The proportion of 5 mg/dL responders during each time interval (Month 3, Month 6, Month 9 and Month 12), defined as subjects achieving and maintaining sUA <5 mg/dL for at least 80% of the time during each time interval.
- The mean change from baseline in sUA at Weeks 14, 24, 36 and 52.
- The time to first sUA > 6 mg/dL.
- The time to two consecutive sUA > 6 mg/dL (stopping rule).
- The percentage of non-hyperuricemic (sUA < 6 mg/dL) time during Months 3, 6, 9 and 12.
- The mean change from baseline in HAQ Pain score at Weeks 14, 24, 36 and 52.
- The mean change from baseline in HAQ Health score at Weeks 14, 24, 36 and 52.
- The mean change from baseline in HAQ-DI score at Weeks 14, 24, 36 and 52.
- The mean change from baseline in tender joint count (68-point scale) at Weeks 14, 24, 36 and 52.
- The mean change from baseline in swollen joint count (66-point scale) at Weeks 14, 24, 36 and 52.
- The mean change from baseline in number of tender or swollen joints at Weeks 14, 24, 36 and 52.
- The mean change from baseline in physician global assessment of gout at Weeks 14, 24, 36 and 52.
- The proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36 and 52.
- The proportion of subjects whose treatment goals are met at Weeks 24 and 52.
- The change from baseline in SBP and DBP to each visit.

Pharmacokinetic and Anti-drug Antibody Endpoints

- PK of pegloticase.
- The incidence of anti-PEG and anti-Uricase IgG antibodies.

Safety and Tolerability Objectives

- AE/SAE profile overall for pegloticase and the combination of pegloticase and MTX
    - Incidence of AESI: IRs, anaphylaxis, gout flares, cardiovascular events
- Laboratory tests
- Vital signs and physical examination

Statistical Analysis on Efficacy Parameters

The primary analysis will be conducted in the Intent-to-Treat (ITT) population, defined as all randomized subjects. The primary efficacy endpoint is the proportion of responders during Month 6. A responder is defined as a subject for whom the proportion of time that the sUA-time curve is <6 mg/dL during the analysis interval is at least 80%. The proportion of time that the sUA level is below 6 mg/dL is defined as the ratio of the time during which the sUA level remains below 6 mg/dL (using linear interpolation, if necessary) to the entire time interval during Month 6. A subject will be declared a non-responder if the subject had an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit prior to or during Month 6. Additionally, a subject who withdraws from study treatment for any reason after randomization and prior to or during Month 6 (for the primary endpoint) or Months 3, 9 or 12 (for the secondary and exploratory endpoints) will be considered a non-responder at the time of withdrawal.

The analysis of the primary responder endpoint will assess risk difference (difference in response proportions) in a stratified analysis. The analysis will use Cochran-Mantel-Haenszel (CMH) weighting to estimate the common risk difference within strata and to estimate the standard error of the common risk difference. Stratification for the analysis will use the same factor as was used to stratify randomization, presence of tophi (yes, no). The difference in response rates, comparing pegloticase with MTX vs. pegloticase with placebo for MTX, will be estimated along with the corresponding 95% confidence interval (CI) and p-value.

The proportion of Month 9 responders and Month 12 responders will be analyzed similarly. The difference in the proportion of subjects with resolution of ≥ 1 tophi (100% decrease in the area of at least 1 tophus) at Week 52 between pegloticase and placebo will be tested with a chi-square test, and the difference in rates will be estimated along with the corresponding 95% CI and p-value.

HAQ-DI score, HAQ Pain and Health scores, tophus size (longest axis), urate volume (DECT), joint erosions due to gout using DECT (hands and feet), joint erosions due to gout using X-ray (hands and feet), swollen/tender joint counts, physician global assessment score, and sUA will be summarized at baseline and each visit with descriptive statistics. Changes from baseline for these parameters to each visit and overall will be analyzed with a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with a term for baseline score, and factors for treatment group, visit, and visit by treatment group interaction. Baseline is defined as the last observation prior to the first dose of MTX. The proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria will be analyzed with a CMH test.

Interim Analysis

An interim analysis will be undertaken when all subjects have been reached the Week 24 visit. An independent DMC will be convened to oversee and interpret this analysis to assess the primary endpoint of maintaining sUA <6 mg/dL at least 80% of the time during Month 6 (Weeks 20, 21, 22, 23 and 24) comparing pegloticase with MTX to pegloticase with placebo for MTX, as well as to assess the safety of the co-administration of pegloticase with MTX based on all accrued data at that time. The DMC will recommend unblinding the Sponsor, stopping the study, or continuing without change at the time of the interim analysis, based on pre-defined criteria. In the event of a highly clinically compelling increase in response rates with pegloticase with MTX vs pegloticase with placebo for MTX, and in the absence of any unexpected safety findings, the Sponsor may become unblinded for full data analysis. Subjects would continue on study through Week 52, with investigators and subjects remaining blinded. Clear parameters to guide decision criteria will be pre-specified in advance. Upon all subjects reaching Week 52, a final analysis would be completed in which the secondary endpoints would be tested, including maintaining sUA <6 mg/dL at least 80% of the time during Month 9, maintaining sUA <6 mg/dL at least 80% of the time during Month 12, and proportion of subjects with complete resolution of at least one tophus by digital photography through Week 24. Additional safety data accrued would also be summarized.

Criteria would also established and pre-specified for the DMC to recommend study discontinuation due to futility or an unexpected safety risk. An interim analysis for futility maybe completed earlier on the basis of the MIRROR Open-Label study results. At the futility analysis there will be no opportunity to conclude a benefit of MTX and therefore there will be no adjustment to the Type I error.

If none of the above scenarios are established, the study would continue and the Sponsor would remain blinded until all subjects reach Week 52.

**Sample Size Estimate**:

The response rate during Month 6 on pegloticase 8 mg every 2 weeks was 43% for the phase 3 studies. A sample size of 135 subjects (90 subjects randomized to receive pegloticase with MTX, 45 subjects randomized to receive pegloticase with placebo for MTX) provides 88% power at the 2-sided alpha=0.05 level to detect a difference of 28% (71% response rate for pegloticase with MTX vs. 43% for pegloticase with placebo for MTX).

## 2.1 Schedule of Assessments

| | Screening[1] | MTX Tolerability Assessment Period/ Run-in Period[2] | | | Pegloticase + IMM Period[3] (Day 1 through Week 24) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening Visit | (-6 wks ±3 d) | (-4 wks ±3 d) | (-2 wks ±3 d) | Day 1 | Wk 2 (±3 d) | Wk 4 (±3 d) | Wk 6 (±3 d) | Wk 8 (±3 d) | Wk 10 (±3 d) | Wk 12 (±3 d) | Wk 14 (±3 d) | Wk 16 (±3 d) | Wk 18 (±3 d) | Wk 20 (±3 d) | Wk 21 (±3 d) | Wk 22 (±3 d) | Wk 23 (±3 d) | Wk 24 (±3 d) |
| **Study Procedure/ Assessment** | | | | | **Inf: 1** | **Inf: 2** | **Inf: 3** | **Inf: 4** | **Inf: 5** | **Inf: 6** | **Inf: 7** | **Inf: 8** | **Inf: 9** | **Inf: 10** | **Inf: 11** | | **Inf: 12** | | **Inf: 13** |
| Informed consent | X | | | | | | | | | | | | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | | | | | |
| Demographic data | X | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | X | | | | | | | | | | | | | | | | |
| Medical/surgical /substance use history[4] | X | | | | | | | | | | | | | | | | | | |
| Medication use history[5] | X | | | | | | | | | | | | | | | | | | |
| Chest X-ray[6] | X | | | | | | | | | | | | | | | | | | |
| Physical examination[7] | X | X | | | X | | X | | X | | X | | X | | X | | | | X |
| Vital signs, height, and weight[8] | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | | X | | X |
| Electrocardiogram[9] | X | | | | | | | | | | | | | | | | | | |
| AE/SAE assessment[10] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Document gout flares and intensity | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Swollen/tender joint counts | | X | | | X | | | X | | | | X | | | X | | | | X |
| HAQ | X | X | | | X | | | X | | | | X | | | X | | | | X |

| | Screening[1] | MTX Tolerability Assessment Period/ Run-in Period[2] | | | Pegloticase + IMM Period[3] (Day 1 through Week 24) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening Visit | (-6 wks ±3 d) | (-4 wks ±3 d) | (-2 wks ±3 d) | Day 1 | Wk 2 (±3 d) | Wk 4 (±3 d) | Wk 6 (±3 d) | Wk 8 (±3 d) | Wk 10 (±3 d) | Wk 12 (±3 d) | Wk 14 (±3 d) | Wk 16 (±3 d) | Wk 18 (±3 d) | Wk 20 (±3 d) | Wk 21 (±3 d) | Wk 22 (±3 d) | Wk 23 (±3 d) | Wk 24 (±3 d) |
| **Study Procedure/ Assessment** | | | | | **Inf: 1** | **Inf: 2** | **Inf: 3** | **Inf: 4** | **Inf: 5** | **Inf: 6** | **Inf: 7** | **Inf: 8** | **Inf: 9** | **Inf: 10** | **Inf: 11** | | **Inf: 12** | | **Inf: 13** |
| Physician global assessment | X | X | | | X | | | X | | | | X | | | X | | | | X |
| DECT[11] | | | | | X | | | | | | | X | | | | | | | X |
| Digital photography[12] | | X | | | X | | | | | | | X | | | | | | | X |
| X-ray of hands and feet[13] | | | | | X | | | | | | | | | | | | | | X |
| MTX/placebo for MTX dosing calendar | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| MTX/placebo for MTX dispensed[14] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| MTX/placebo for MTX dosing[14] | | Once weekly from Week -6 until prior to the Week 52 Visit, inclusive | | | | | | | | | | | | | | | | | |
| Gout prophylaxis Rxs filled[15] | | Rxs filled as needed | | | | | | | | | | | | | | | | | |
| Fexofenadine Rx filled[16] | | Rxs filled as needed | | | | | | | | | | | | | | | | | |
| Folic acid Rx filled[17] | | Rxs filled as needed | | | | | | | | | | | | | | | | | |
| MTX/placebo for MTX compliance/ reconciliation | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X |
| Infusion reaction prophylaxis[18] | | | | | X | X | X | X | X | X | X | X | X | X | X | | X | | X |
| IR prophylaxis compliance (Yes/No) | | | | | X | X | X | X | X | X | X | X | X | X | X | | X | | X |

| | Screening[1] | MTX Tolerability Assessment Period/ Run-in Period[2] | | | Pegloticase + IMM Period[3] (Day 1 through Week 24) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening Visit | (-6 wks ±3 d) | (-4 wks ±3 d) | (-2 wks ±3 d) | Day 1 | Wk 2 (±3 d) | Wk 4 (±3 d) | Wk 6 (±3 d) | Wk 8 (±3 d) | Wk 10 (±3 d) | Wk 12 (±3 d) | Wk 14 (±3 d) | Wk 16 (±3 d) | Wk 18 (±3 d) | Wk 20 (±3 d) | Wk 21 (±3 d) | Wk 22 (±3 d) | Wk 23 (±3 d) | Wk 24 (±3 d) |
| **Study Procedure/ Assessment** | | | | | **Inf: 1** | **Inf: 2** | **Inf: 3** | **Inf: 4** | **Inf: 5** | **Inf: 6** | **Inf: 7** | **Inf: 8** | **Inf: 9** | **Inf: 10** | **Inf: 11** | | **Inf: 12** | | **Inf: 13** |
| Folic acid/gout flare prophylaxis compliance (Yes/No) | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X |
| Pegloticase infusion | | | | | X | X | X | X | X | X | X | X | X | X | X | | X | | X |
| Pegloticase PK sampling[19] | | | | | X | X | | X | | | | X | | | | X | | | X |
| Pre-infusion MTX Polyglutamate sampling | | | | | X | | | | | | | X | | | | | | | X |
| sUA[20] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology sample | X | X | X | X | X | X | | X | | | | X | | | | | X | | X |
| Clinical chemistry sample | X | X | X | X | X | X | | X | | | | X | | | | | X | | X |
| Spot urine collection | | | | | X | | | | | | | X | | | | | | | X |
| Antibody sample[21] | | | | | X | X | | X | | | | X | | | | | X | | X |
| Additional samples for future analysis [22] | | X | | | X | X | X | X | X | X | X | X | | | | | | | X |
| G6PD test | X | | | | | | | | | | | | | | | | | | |
| Pregnancy test[23] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X |
| PI assessment of subject clinical status and subject treatment goals[24] | X | | | | | | | | | | | | | | | | | | X |

| | Pegloticase + IMM Period[3] (Week 26 through Week 50) | | | | | | | | | | | | | End of Pegloticase Infusions Visit[26] (if applicable) | End of Study/ Early Termin-ation | Safety Follow-up Phone/ Email Visit | MTX Partner Pregnancy Follow-up | Post Treatment Follow-up[27] (if applicable) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Wk 26 (±3 d)** | **Wk 28 (±3 d)** | **Wk 30 (±3 d)** | **Wk 32 (±3 d)** | **Wk 34 (±3 d)** | **Wk 36 (±3 d)** | **Wk 38 (±3 d)** | **Wk 40 (±3 d)** | **Wk 42 (±3 d)** | **Wk 44 (±3 d)** | **Wk 46 (±3 d)** | **Wk 48 (±3 d)** | **Wk 50 (±3 d)** | **Within 2 weeks following final infusion if prior to Wk 50** | **Wk 52 (±3 d)** | **30 days after last pegloticase infusion (±3 d)** | **approx. 3 months after last MTX dose** | **3 Month and 6 Month** |
| **Study Procedure/ Assessment** | **Inf: 14** | **Inf: 15** | **Inf: 16** | **Inf: 17** | **Inf:18** | **Inf: 19** | **Inf: 20** | **Inf: 21** | **Inf: 22** | **Inf: 23** | **Inf: 24** | **Inf: 25** | **Inf: 26** | | | | | |
| Physical examination[7] | | | | | | X | | | | | | | | X | X | | | X |
| Vital signs, height, and weight[8] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X |
| AE/SAE assessment[10] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X |
| Document gout flares and intensity | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X |
| Swollen/tender joint counts | | | X | | | X | | | | X | | | | X | X | | | X |
| HAQ | | | X | | | X | | | | X | | | | X | X | | | X |
| Physician global assessment | | | X | | | X | | | | X | | | | X | X | | | X |
| DECT[11] | | | | | | | | | | | | | | X | X | | | |
| Digital photography[12] | | | | | | X | | | | | | | | X | X | | | X |
| X-ray of hands and feet[13] | | | | | | | | | | | | | | X | X | | | |

| | Pegloticase + IMM Period[3] (Week 26 through Week 50) | | | | | | | | | | | | | End of Pegloticase Infusions Visit[26] (if applicable) | End of Study/ Early Termin-ation | Safety Follow-up Phone/ Email Visit | MTX Partner Pregnancy Follow-up | Post Treatment Follow-up[27] (if applicable) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Wk 26 (±3 d)** | **Wk 28 (±3 d)** | **Wk 30 (±3 d)** | **Wk 32 (±3 d)** | **Wk 34 (±3 d)** | **Wk 36 (±3 d)** | **Wk 38 (±3 d)** | **Wk 40 (±3 d)** | **Wk 42 (±3 d)** | **Wk 44 (±3 d)** | **Wk 46 (±3 d)** | **Wk 48 (±3 d)** | **Wk 50 (±3 d)** | **Within 2 weeks following final infusion if prior to Wk 50** | **Wk 52 (±3 d)** | **30 days after last pegloticase infusion (±3 d)** | **approx. 3 months after last MTX dose** | **3 Month and 6 Month** |
| **Study Procedure/ Assessment** | **Inf: 14** | **Inf: 15** | **Inf: 16** | **Inf: 17** | **Inf:18** | **Inf: 19** | **Inf: 20** | **Inf: 21** | **Inf: 22** | **Inf: 23** | **Inf: 24** | **Inf: 25** | **Inf: 26** | | | | | |
| MTX/placebo for MTX dosing calendar | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| MTX/placebo for MTX dispensed[14] | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| MTX/placebo for MTX dosing[14] | Once weekly from Week -6 to prior to the Week 52 Visit, inclusive | | | | | | | | | | | | | | | | | |
| Gout prophylaxis Rxs filled[15] | Rxs filled as needed | | | | | | | | | | | | | | | | | |
| Fexofenadine Rx filled[16] | Rxs filled as needed | | | | | | | | | | | | | | | | | |
| Folic acid Rx filled[17] | Rxs filled as needed | | | | | | | | | | | | | | | | | |
| MTX/placebo for MTX compliance/ reconciliation | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Infusion reaction prophylaxis[18] | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| IR prophylaxis compliance (Yes/No) | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |

| | Pegloticase + IMM Period[3] (Week 26 through Week 50) | | | | | | | | | | | | | End of Pegloticase Infusions Visit[26] (if applicable) | End of Study/ Early Termin-ation | Safety Follow-up Phone/ Email Visit | MTX Partner Pregnancy Follow-up | Post Treatment Follow-up[27] (if applicable) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Wk 26 (±3 d)** | **Wk 28 (±3 d)** | **Wk 30 (±3 d)** | **Wk 32 (±3 d)** | **Wk 34 (±3 d)** | **Wk 36 (±3 d)** | **Wk 38 (±3 d)** | **Wk 40 (±3 d)** | **Wk 42 (±3 d)** | **Wk 44 (±3 d)** | **Wk 46 (±3 d)** | **Wk 48 (±3 d)** | **Wk 50 (±3 d)** | **Within 2 weeks following final infusion if prior to Wk 50** | **Wk 52 (±3 d)** | **30 days after last pegloticase infusion (±3 d)** | **approx. 3 months after last MTX dose** | **3 Month and 6 Month** |
| **Study Procedure/ Assessment** | **Inf: 14** | **Inf: 15** | **Inf: 16** | **Inf: 17** | **Inf:18** | **Inf: 19** | **Inf: 20** | **Inf: 21** | **Inf: 22** | **Inf: 23** | **Inf: 24** | **Inf: 25** | **Inf: 26** | | | | | |
| Folic acid/gout flare prophylaxis compliance (Yes/No) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Pegloticase infusion | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| Pegloticase PK sampling[19] | | | | | | X | | | | | | | | X | X | | | |
| Pre-infusion MTX Polyglutamate sampling | | | | | | X | | | | | | | | | | | | |
| sUA[20] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X |
| Hematology | | | | | | X | | | | | | | | X | X | | | X |
| Clinical chemistry | | | | | | X | | | | | | | | X | X | | | X |
| Spot urine collection | | | | | | X | | | | | | | | X | X | | | |
| Antibody testing[21] | | | | | | X | | | | | | | | X | X | | | X |
| Additional samples for future analysis[22] | | | | | | X | | | | | | | | X | X | | | |
| Pregnancy test[23] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |

| | Pegloticase + IMM Period[3] (Week 26 through Week 50) | | | | | | | | | | | | | End of Pegloticase Infusions Visit[26] (if applicable) | End of Study/ Early Termin-ation | Safety Follow-up Phone/ Email Visit | MTX Partner Pregnancy Follow-up | Post Treatment Follow-up[27] (if applicable) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Wk 26 (±3 d)** | **Wk 28 (±3 d)** | **Wk 30 (±3 d)** | **Wk 32 (±3 d)** | **Wk 34 (±3 d)** | **Wk 36 (±3 d)** | **Wk 38 (±3 d)** | **Wk 40 (±3 d)** | **Wk 42 (±3 d)** | **Wk 44 (±3 d)** | **Wk 46 (±3 d)** | **Wk 48 (±3 d)** | **Wk 50 (±3 d)** | **Within 2 weeks following final infusion if prior to Wk 50** | **Wk 52 (±3 d)** | **30 days after last pegloticase infusion (±3 d)** | **approx. 3 months after last MTX dose** | **3 Month and 6 Month** |
| **Study Procedure/ Assessment** | **Inf: 14** | **Inf: 15** | **Inf: 16** | **Inf: 17** | **Inf:18** | **Inf: 19** | **Inf: 20** | **Inf: 21** | **Inf: 22** | **Inf: 23** | **Inf: 24** | **Inf: 25** | **Inf: 26** | | | | | |
| PI assessment of subject clinical status and subject treatment goals[24] | | | | | | | | | | | | | | X | X | | | |
| Partner pregnancy[25] | | | | | | | | | | | | | | | | | X | |

AE = adverse event; d = day(s); Inf = infusion; DECT = dual-energy computed tomography; G6PD = glucose-6-phosphate dehydrogenase; HAQ = Health Assessment Questionnaire; IR = infusion reaction; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; PK = pharmacokinetic; Rx = prescription; sUA = serum uric acid; V= Visit; wk(s) = week(s); IMM = Immunomodulator

Footnotes:

1. The Screening Visit can occur any time within 4 weeks prior to the first dose of MTX at Week -6.
2. During the MTX Tolerability Assessment Period (Week -6 until the Week -4 visit), all subjects will take MTX 15 mg orally weekly. At the Week -4 visit, subjects who tolerated methotrexate will be randomized to receive MTX 15 mg or placebo for MTX orally weekly. Subjects will be blinded to MTX or placebo for MTX beginning at Week -4 through the remainder of the study. Subjects will continue to take the blinded MTX or placebo for MTX during the Run-in Period (from Week -4 to Day 1) at the 15 mg MTX dose or placebo for MTX dose. If a subject does not tolerate the 15 mg MTX or placebo for MTX dose after randomization at the Week -4 Visit and prior to Day 1, the MTX or placebo for MTX may be dose-reduced or discontinued based on pre-specified criteria and after discussion with the Sponsor medical monitor. The subject will be allowed to remain in the study.
3. 52-week Pegloticase + MTX or Pegloticase + placebo for MTX Period.
4. The Investigator or designee will collect a complete gout history and other relevant medical/surgical/substance use history.
5. Medication history will be collected at Screening. History of all prior gout medications will be collected. History of non-gout medication use in the year prior to Screening will be collected.

6. Subjects that do not have a chest X-ray within 2 years prior to Screening will have an X-ray done during Screening, if deemed necessary by the Investigator.
7. A complete physical examination will be performed at the Screening Visit, including assessment of HEENT, heart, lungs, abdomen, skin, extremities, neurological status and musculoskeletal including an assessment for the presence of tophi. A targeted physical examination per investigator judgement will be conducted at Week -6, Day 1, and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20, 24, 36 and the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and 3 and 6 month Post Treatment Follow-up Visits; at a minimum this should include heart, lungs, and abdominal exam. Clinically significant findings from the targeted physical examinations will be recorded as AEs.
8. Routine vital signs, including blood pressure, respiratory rate, temperature, and heart rate will be measured at Screening, Week -6, Week -4, Day 1 and Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and the End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and 3 and 6 month Post Treatment Follow-up Visits. Heart rate and blood pressure measurements should be taken after the subject has been in a sitting position and in a rested and calm state with proper positioning including back support, feet flat on the floor, for at least 5 minutes. Subjects arm should be supported at heart level; and cuff placed on the bare arm. A large cuff should be used as needed to fit the upper arm and a consistent arm is to be used at each study visit. The Korotkoff phase V will be used to determine diastolic blood pressure. During the Pegloticase + IMM Period study visits, vitals should be taken before the pegloticase infusion and any time after the end of the infusion, but prior to subject's discharge/release from the site. At sites who participate and from subjects who consent, optional intensive BP collections will be obtained at designated timepoints. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained. Optional intensive blood pressure measurements will be taken prior to the infusion on Day 1 and at Weeks 6, 12, 18, 24, 30, 36, 42, 48 and at the non-infusion End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visit. At these intensive blood pressure collections, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained. All 3 values will be recorded in the eCRF. When possible, the same staff member should take all BP measurements for a given subject. Weight should be measured in kilograms or pounds without shoes and recorded at the Screening Visit and prior to dosing MTX Week -6 Visit; prior to pegloticase infusion on Day 1 and at the Weeks 8, 16, 24, 36 and at the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and Months 3 and 6 Post Treatment Follow-up Visits. Height will be collected at the Screening Visit only.
9. Electrocardiogram should be completed during Screening. The Electrocardiogram is read at the site.
10. AEs/SAEs will be collected from the signature of the ICF until the 6 month Post Treatment Follow-up Visit. For each AE, the Investigator will be asked to record if the event was possibly an infusion reaction or anaphylaxis and if so, will be prompted to complete additional eCRFs. Females of childbearing potential will be asked to confirm if ovulation has occurred since the last dose of MTX or placebo for MTX. If the subject had not ovulated a urine pregnancy test will be required.
11. For sites with DECT capability and subjects who provide consent, an optional DECT will be obtained at Day 1 and Weeks 14, 24 and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination. The DECT may be completed within +/- 5 days of the scheduled timepoint. Subjects who end pegloticase infusions prior to Week 52 should follow the scheduled timepoints but avoid a repeat DECT scan within 6 weeks of a prior scan (detailed guidance is provided with the imaging manual).
12. Digital photography will be completed at Week -6, Day 1 and Weeks 14, 24, 36, and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination and the 3 and 6 month Post Treatment Follow-up Visits. Digital photography of hands and feet will be performed according to the instructions provided in the digital photography manual. Other anatomical sites with large tophi may be photographed in addition to the hands and feet at the Investigator's discretion.
13. For sites with X-ray capability and subjects who provide consent, an optional X-ray of the hands and feet will be obtained at Day 1, Week 24 and End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visit. Subjects who end pegloticase infusions prior to Week 52 should follow the scheduled timepoints but avoid a repeat X-ray within 3 months of a prior X-ray (detailed guidance is provided with the imaging manual).
14. MTX or placebo for MTX will be dispensed and brought back to check compliance. MTX or placebo for MTX should be taken 1 to 3 days prior to each pegloticase infusion; however, if a subject does not do so, MTX or placebo for MTX must be taken ≥60 minutes prior to each pegloticase infusion.
15. It is required that before a subject begins the pegloticase + IMM Period, he or she has been taking at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone <10 mg/day) for ≥1 week before the first dose of pegloticase and continues flare prophylaxis per American College of Rheumatology guidelines [Khanna D et al. 2012] for the greater of 1) 6 months, 2) 3 months after achieving target serum urate (sUA < 6 mg/dL) for

patients with no tophi detected on physical exam, or 3) 6 months after achieving target serum urate (sUA < 5 mg/dL) for patients with one or more tophi detected on initial physical exam that have since resolved.

16. For IR prophylaxis, fexofenadine (180 mg orally) will be taken the day before and the morning of just prior to each infusion.
17. Subjects will take folic acid 1 mg orally every day beginning at Week -6 (the start of MTX) until prior to the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of Study/Early Termination.
18. Infusion reaction prophylaxis includes fexofenadine (180 mg orally) administered the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) administered on the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, immediately prior to each infusion.
19. For all subjects, serum samples for PK analysis will be collected after the end of infusion on Day 1 (prior to discharge); prior to the pegloticase infusion and after the end of infusion (prior to discharge) at the Weeks 2, 6, 14, 24, 36; and at the non-infusion Week 21 Visit and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visits.
20. Serum samples for measurement of sUA levels will be collected at the Screening Visit, the Week -6 Visit (prior to the first dose of MTX), the Week -4 Visit (Randomization) and the Week -2 Visit during the Run-in Period; within 48 hours prior to each pegloticase infusion and after the end of each pegloticase infusion prior to discharge from the site during the Pegloticase + IMM Period on Day 1, at the Weeks 2, 6, 10, 12, 14, 20, 22, 24, 32, 34, 36, 48 and 50; within 48 hours prior to each pegloticase infusion at Weeks 4, 8, 16, 18, 26, 28, 30, 38, 40, 42, 44 and 46. Additional serum samples for sUA levels will be collected at non-infusion Visits at Weeks 21 and 23 and the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of study/Early Termination Visit and 3 and 6 month Follow-up Visits. Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue pegloticase and complete the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of study/Early Termination Visit procedures. Two separate samples/tubes of blood should be collected within 48 hours prior to the pegloticase infusion (except on Day 1 when only 1 pre-infusion sample is required for the central laboratory). One sample/tube will be assessed by the site's local laboratory to be used for on-study subject management; pre-infusion sUA results must be reported by the local or central laboratory prior to each pegloticase infusion. If a local laboratory sample is drawn (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit. The second sample/tube will be sent to the central laboratory for analysis and recording in the database. See the Laboratory Manual for instructions for alternate scenarios. In the event of an AE suspected to be an infusion reaction, a serum sample will be collected at that time or at the subsequent visit for evaluation of pegloticase antibodies.
21. Serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 2, 6, 14, 22, 24, 36; and at the non-infusion End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of Study/Early Termination Visit and Month 3 Post Treatment Follow-up Visits.
22 For subjects who provide consent, optional blood samples for PBMC, RNA isolation and serum will be collected from each consenting subject prior to the first dose of MTX on -6 week, prior to the infusion at Day 1 and Weeks, 6, 14, 24, 36 and the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End-of-Study/Early Termination. During visits at Weeks 2, 4, 8, 10 and 12, optional samples will only be collected if subjects are experiencing an acute gout flare on the day of visit.
23. For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit. A urine pregnancy test will be performed 30 days after the last MTX or placebo for MTX dose if the subject has not ovulated; at the End of Pegloticase Infusions Visit (if applicable), the Week 52/End of study/Early Termination Visit procedures and at the 30 day follow up phone/e-mail visit it is determined that the subject has not ovulated since the last dose of MTX or placebo for MTX; a urine pregnancy test will be performed at all other indicated visits.
24. The Investigator will review the clinical status and individual subject treatment goals at Screening, Week 24, and the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of study/Early Termination Visit.
25. Subjects who are non-vasectomized males will be asked 3 months after MTX or placebo for MTX discontinuation regarding partner pregnancy. This will occur at a regulatory scheduled visit or by a separate phone/email visit.
26. Subjects who end treatment due to the stopping rules or other reasons should complete the End of Pegloticase Treatment Visit within 2 weeks of the last infusion. Subjects should remain on study. See Section 9.3.3.1.1 for details on visits and procedures.
27. All subjects will be followed for a minimum of 6 months following treatment following the end of pegloticase infusions.

# 3 TABLE OF CONTENTS

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# 4 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| CFR | Code of Federal Regulations |
| DECT | dual-energy computed tomography |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| FDA | Food and Drug Administration |
| G6PD | glucose-6-phosphate dehydrogenase |
| GCP | Good Clinical Practice |
| HAQ | Health Assessment Questionnaire |
| HAQ-DI | Health Assessment Questionnaire – Disability Index |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IMM | immunomodulator |
| IND | Investigational New Drug |
| IR | infusion reaction |
| IRB | Institutional Review Board |
| IV | intravenous(ly) |
| mITT | modified intention-to-treat |
| MTX | methotrexate |
| NSAID | non-steroidal anti-inflammatory drug |
| PK | pharmacokinetic(s) |
| PO | oral |
| PBMC | peripheral blood mononuclear cell |
| RNA | ribonucleic acid |
| RTSM | Randomization and Trial Supply Management |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| sUA | serum uric acid |
| ULT | urate lowering therapy |
| USP | United States Pharmacopeia |

Note: Abbreviations used only once in a paragraph or in tables or figures are defined within the relevant paragraph, table, or figure.

# 5 ETHICS

## 5.1 Institutional Review Board/Independent Ethics Committee

The Principal Investigator (Investigator), the Sponsor and/or designee authorized by the Sponsor will submit this protocol, any protocol modifications, the informed consent form (ICF), and all applicable study documentation to be used in this study to the appropriate Institutional Review Board (IRB) for review and approval/favorable opinion. A letter confirming the IRB approval/favorable opinion of the protocol, the subject ICF, and applicable study documentation, a list of the IRB members involved in the vote, as well as a statement that the IRB is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations, must be forwarded to the Sponsor or its designee **prior to** the enrollment of subjects into the study. A copy of the approved ICF will also be forwarded to the Sponsor or its designee. Appropriate reports on the progress of the study will be made to the IRB and the Sponsor or its designee by the Investigator in accordance with applicable governmental regulations and in agreement with the policy established by the Sponsor.

## 5.2 Ethical Conduct of the Study

The Investigators will ensure that this study is conducted in a manner that fully conforms with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined by International Council for Harmonisation (ICH) Tripartite Guideline for GCP or with local law if it affords greater protection to the subject. The Investigator will additionally ensure adherence to the basic principles of GCP, as outlined in the current version of 21 Code of Federal Regulations (CFR), subchapter D, part 312, “Responsibilities of Sponsors and Investigators,” part 50, “Protection of Human Subjects,” and part 56, “Institutional Review Boards.”

## 5.3 Subject Information and Consent

It is the responsibility of the Investigator or a person designated by the Investigator (if acceptable by local regulations) to obtain a signed ICF from each subject prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

The Investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The ICF and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject’s consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written ICF. The Investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IRB`s approval/favorable opinion in advance of use.

All signed ICFs are to remain in the Investigator's site file or, if locally required, in the subjects' notes/files of the medical institution.

The electronic case report forms (eCRFs) for this study contain a section for documenting all subject ICFs, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the ICF should be reviewed and updated, if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised ICF, and give their consent to continue in the study.

### 5.4 Compensation for Health Damage of Subjects/Insurance

The Sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

### 5.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the Sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The Investigator will maintain a list to enable subjects to be identified.

The Sponsor will ensure that the use and disclosure of protected health information obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (HIPAA).

## 6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Sponsor of this study is Horizon Pharma Rheumatology LLC (Horizon). Horizon personnel will serve as the Medical Monitor and the Sponsor's regulatory representative (see Section 17.1 for details). The Sponsor's regulatory representative will be responsible for timely reporting of serious adverse events (SAEs) to regulatory authorities, as required. The Sponsor will be responsible for timely reporting of SAEs and any other new pertinent safety information to all Investigators, as required.

The study will be conducted at approximately 65 study centers in the United States. Prior to initiation of the study, each Investigator will provide the Sponsor or its designee with a fully executed and signed Food and Drug Administration (FDA) Form 1572 and a Financial Disclosure Form. Financial Disclosure Forms will also be completed by all sub-investigators listed on the Form 1572. It is the responsibility of the Investigators or sub-investigators to advise the Sponsor of any change in the relevant financial interests that occur during the study and the 1-year period following its completion.

Table 6.1 lists organizations that are critical to the conduct of the study, with a brief description of their roles:

**Table 6.1 Table of Non-Sponsor Study Responsibilities**

| Study Responsibility | Organization |
|---|---|
| Clinical drug supply and distribution | PCI Pharma Services<br>4545 Assembly Drive<br>Rockford, IL 61109 |
| Central safety laboratory | Covance Central Laboratory Services<br>8211 SciCor Drive<br>Indianapolis, IN 46214 |
| Data Management | Medidata<br>350 Hudson Street, 9th Floor<br>New York, NY 10014 |
| Statistics | Syneos<br>1030 Sync Street<br>Morrisville, NC 27560 |
| DMC/Adjudication Committee | AXIO<br>2601 4th Avenue, Suite 200<br>Seattle, WA 98121 |
| Central imaging vendor | Bioclinica<br>211 Carnegie Center Drive<br>Princeton, NJ 08540 |

# 7 INTRODUCTION

## 7.1 Background

### 7.1.1 Gout

Gout affects approximately 4% of the United States population, is the most common form of inflammatory arthritis in men, and is associated with decreased quality of life [Saag and Choi, 2006; Singh and Strand, 2008; Zhu et al, 2011; Sattui et al, 2014]. The frequency of gout is increasing worldwide, with prevalence rates estimated to be as high as 7% in older men [Mikuls et al, 2005; Saag and Choi, 2006; Roddy and Doherty, 2010]. While the exact prevalence is unknown, as many as 200,000 persons in the United States experience chronic symptoms of gout, which is sometimes referred to as chronic refractory gout, despite trials of oral urate-lowering therapy. This is characterized by ongoing symptoms of active disease and a failure to control/maintain serum uric acid (sUA) <6 mg/dL with conventional xanthine oxidase

inhibitors (i.e., allopurinol and febuxostat) and uricosuric agents (i.e., probenecid) [AAC Briefing Document 2009; Brook et al, 2010; Wertheimer et al, 2013; Khanna et al, 2016]. These patients often have significant, disabling urate deposits in soft tissues and bone known as tophi.

### 7.1.2 Pegloticase

Pegloticase (KRYSTEXXA, a recombinant modified mammalian urate oxidase [uricase]), is indicated for treatment-failure gout (TFG) to control hyperuricemia and to manage the signs and symptoms of gout. Pegloticase was granted orphan designation by the FDA on 21 February 2001 (ODA #00-1356) and pegloticase 8 mg every 2 weeks was approved by the FDA on 14 September 2010 for the treatment of adult patients with chronic gout refractory to conventional therapy.

Two replicate pivotal phase 3 studies for pegloticase were undertaken to establish the efficacy and safety of the product. The primary endpoint was defined as plasma UA (highly correlated to serum uric acid) reduction to below 6 mg/dL for 80% of the time in Months 3 and 6 combined. The pooled response rate for pegloticase 8 mg every two weeks was 42%, versus a placebo response rate of 0%. There was also a greater reduction in complete resolution of ≥ 1 tophus in the every 2 weeks dosing group, and favorable effect of pegloticase treatment in the reduction of the number of tender and swollen joints. In subsequent open-label extension studies, pegloticase led to continued control of pUA, reduction in gout flares, and continued resolution of tophi, suggesting continuing benefit with extended pegloticase treatment beyond the initial 6 months of therapy, particularly in subjects who met responder criteria in the placebo-controlled trials.

In the phase 3 pivotal studies, deaths, AEs, SAEs, as well as the laboratory abnormalities were generally equally distributed across placebo and pegloticase treatment groups, with the clear exception of gout flares and infusion reactions. Pegloticase-treated subjects exhibited a higher rate of gout flares during Months 1-3 as uric acid was being acutely lowered, then a decrease in gout flares vs. placebo during Months 4-6. Despite use of prophylactic medications against hypersensitivity including administration of corticosteroids, antihistamine, and acetaminophen in advance of each pegloticase infusion, infusion reactions were seen in 22/85 (26%) of subjects receiving the 8 mg 2 week regimen. There was no specified definition of anaphylaxis in the Phase 3 protocols, and there were no investigator-reported events of anaphylaxis in the Phase 3 studies with pegloticase. However, in a post-hoc review applying the NIAID/FAAN criteria (Sampson et al., 2006), it was determined that across the Phase 2 and Phase 3 program, anaphylaxis occurred in 6.5% of subjects treated with pegloticase dosed every 2 weeks. Anaphylaxis generally occurred within 2 hours after treatment. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. All of these events had relatively rapid resolution with the cessation of infusion.

In a post-hoc analysis, the apparent role of immunogenicity in both loss of urate lowering effect and incidence of infusion reactions was appreciated. Only 2% of subjects with anti pegloticase antibody titers exceeding 1:2430 maintained a urate-lowering response to pegloticase compared with 63% of subjects who were treated for at least 2 months without developing high-titer antibodies ($p < 0.001$) (Sundy et al., 2011). The incidence of IRs was higher among subjects who

developed high-titer antibodies compared with those who had titers that did not exceed 1:2430 (60% vs 19%; $p < 0.001$) (Sundy et al., 2011). In addition, most IRs occurred when sUA levels were greater than 6 mg/dL. Retrospective analyses showed that the loss of urate-lowering efficacy, as reflected by sUA of greater than 6 mg/dL, preceded a patient's first IR, whenever it occurred, in 20 (91%) of 22 subjects treated with pegloticase every 2 weeks.

Reducing anti-drug antibodies with concomitant administration of the immunomodulatory agent methotrexate (MTX) has been shown to be useful with other infused products that lead to immunogenicity, such as infliximab, in the setting of rheumatoid arthritis treatment. This study will test whether the loss of sUA response to pegloticase can be prevented or delayed by the pre-treatment and concomitant use of MTX with pegloticase compared to pegloticase alone [Hershfield et al, 2014].

#### 7.1.2.1 Physiochemical Properties

Pegloticase is a uric acid-specific enzyme that is a monomethoxy-poly(ethylene glycol) (PEG)ylated product consisting of recombinant modified mammalian urate oxidase (uricase) produced by a genetically modified strain of *Escherichia coli*. Uricase is covalently conjugated to methoxy PEG (mPEG) (10 kDa molecular weight). The cDNA coding for uricase is based on mammalian sequences. Each uricase subunit has a molecular weight of approximately 34 kDa. The average molecular weight of pegloticase (tetrameric enzyme conjugated to mPEG) is approximately 545 kDa.

| | |
|---|---|
| **INN:** | Pegloticase |
| **Chemical name (INN):** | Oxidase, urate (synthetic *Sus scrofa* variant pigKS-ΔN subunit), homotetramer, amide with α-carboxy-ω-methoxypoly(oxy-1,2-ethanediyl) |
| **National drug code (NDC):** | 75987-080-10 |
| **CAS number** | 885051-90-1 |
| **Molecular formula:** | $C_xH_yN_{1632}O_zS_{32}$<br>Wherein, x = ~22,920, y = ~43,095, z = ~10,191 |
| **Molecular weight:** | Monomer pegloticase approximately 545 kDa<br>*(based on the estimation of amino acid sequence of uricase and an average of 10.2 strands of approximately 10 kDa monomethoxypoly(ethylene glycol) (mPEG) per uricase monomeric subunit. The monomethoxypoly(ethylene glycol) strands attached to the uricase protein comprise approximately three-quarters of the molecular weight of pegloticase.)* |
| **Chemical Structural Formula:** | $\{[H_3C\text{-}O\text{-}(CH_2CH_2\text{-}O)_m\text{-}CO\text{-}]_n\text{-}NH\text{-}$<br>[TYKKNDEVEF VRTGYGKDMI KVLHIQRDGK YHSIKEVATT VQLTLSSKKD<br>YLHGDNSDVI PTDTIKNTVN VLAKFKGIKS IETFAVTICE HFLSSFKHVI<br>RAQVYVEEVP WKRFEKNGVK HVHAFIYTPT GTHFCEVEQI RNGPPVIHSG<br>IKDLKVLKTT QSGFEGFIKD QFTTLPEVKD RCFATQVYCK WRYHQGRDVD<br>FEATWDTVRS IVLQKFAGPY DKGEYSPSVQ KTLYDIQVLT LGQVPEIEDM<br>EISLPNIHYL NIDMSKMGLI NKEEVLLPLD NPYGKITGTV KRKLSSRL]$\}_4$<br>Wherein, m=~225, n=~10.2 and each uricase monomeric subunit having the amino acid sequence listed above.<br>Approximately 10.2 units of methoxypoly(ethylene glycol) are attached to Lysine(K) residues per uricase monomeric subunit. |
| **Appearance:** | Clear colorless solution, free of visible particles. |

#### 7.1.2.2 Safety Pharmacology

Unlike most mammalian species, humans lack the urate oxidase enzymatic pathway for the oxidation and disposition of uric acid and are susceptible to the development of gout. To develop an animal model of hyperuricemia and gout for a therapeutic uricase proof-of-concept study, a mouse was genetically modified by knocking out its endogenous uricase gene (*Uox*). This genetic lesion results in a marked elevation of plasma uric acid levels, leading to deposition of urate in kidney tissue and causing a profound defect in renal concentrating ability and nephrogenic diabetes insipidus. The studies in the mouse *Uox-/-* system demonstrate the therapeutic potential of pegloticase administration for the treatment of hyperuricemia and provided a “proof of principle” for the clinical use of pegloticase.

In addition, in nonclinical toxicity studies in which uric acid levels were measured, a decline in uric acid levels following administration of pegloticase (all pegloticase doses associated with these studies) was observed.

The results from the acute and chronic toxicity studies did not indicate any toxic or adverse effect of pegloticase administered with a human exposure 645 times higher than that in the Phase 3 clinical studies (8 mg every 2 weeks) based on the area under the curve values from the 39-week, repeat-dose, dog study (high-dose).

An observation in the chronic toxicology studies is the finding of a dose-dependent increase in vacuolated cells. There were no associated clinical manifestations in any animals in which vacuolated cells were present. Evidence of vacuolated cells, especially in the spleen, has been observed with pegloticase administration in all the chronic toxicity studies as well as the embryo/fetal development and absorption, distribution, metabolism, and excretion studies in the rat. It is thought that vacuolation of spleen macrophages is a result of lysosomal overloading following phagocytosis of persistent circulating macromolecules of high molecular weight. In the 39-week, long-term toxicity studies in dogs, vacuolated cells were also present in the basal area of the lamina propria within the duodenum and jejunum, adrenal cortical cells, hepatic Kupffer cells, and the intimal cells within the aortic outflow area of the heart. The vacuolated cells in the heart and adrenal gland did not stain as macrophages. In the aortic outflow tract of the heart, vacuoles were seen in the cytoplasm of endothelial cells in the intimal lining of the aorta. In the adrenal gland, vacuoles were located within cortical cells in the zona reticularis and zona fasciculata. The clinical significance of these findings and functional consequences are unknown.

Refer to the current version of the KRYSTEXXA Investigator's Brochure for detailed information.

#### 7.1.2.3 Non-clinical Pharmacokinetics

A series of pharmacokinetic (PK) studies was conducted in rats, rabbits, dogs, and pigs to determine the circulation half-life and bioavailability as a function of the route of pegloticase administration. Plasma pegloticase levels were determined by assaying uricase bioactivity in plasma. As part of the PK studies, antibody levels in plasma were determined 2 weeks after the last injection in the rabbit, dog, and rat. Collectively, the results of the PK studies in these animals lend support to the expectation of high bioavailability and prolonged retention of pegloticase after administration in humans.

Absorption, distribution, metabolism, and excretion of pegloticase were examined in rat studies. Approximately 70% of the dose was excreted in the urine during the course of 7 days after injection.

Refer to the current version of the KRYSTEXXA Investigator's Brochure for detailed information.

#### 7.1.2.4 Pharmacokinetics

Pegloticase levels were determined in serum based on measurements of uricase enzyme activity.

Following single IV infusions of 0.5 mg to 12 mg pegloticase in 23 patients with symptomatic gout, maximum serum concentrations of pegloticase increased in proportion to the dose administered.

The PK of pegloticase has not been studied in children and adolescents.

In patients undergoing hemodialysis (Study M0403), pegloticase serum concentrations were not clinically meaningfully affected by 2 hemodialysis sessions. Pre- and post-dialyzer samples, as well as samples taken during dialysis, demonstrated that study drug was not removed by the dialysis process.

No formal studies have been conducted to examine the effects of hepatic impairment on pegloticase PK.

#### 7.1.2.5 Risks of Pegloticase

The risks of pegloticase use are detailed in the full prescribing information and include:

- Infusion Reactions (IRs), including anaphylaxis
- Hemolysis and methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Gout flares
- Congestive heart failure exacerbation

Subjects with diseases or conditions (e.g., non-compensated congestive heart failure) that could potentially place them at increased risk for these events will be excluded from the study.

It is required that all subjects receive prophylactic treatment to reduce the risk of acute gout flares, unless medically contraindicated or not tolerated, as noted in the pegloticase prescribing information. Subjects will begin at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone <10 mg/day) for ≥1 week before the first dose of pegloticase and should continue flare prophylaxis per American College of Rheumatology guidelines [Khanna D et al.2012] for the greater of 1) 6 months, 2) 3 months after achieving target serum urate (sUA < 6 mg/dL) for patients with no tophi detected on physical exam, or 3) 6 months after achieving target serum urate (sUA < 5 mg/dL) for patients with one or more tophi detected on initial physical exam that have since resolved.

Since IRs can occur, all subjects will receive pre-treatment prophylaxis consisting of an antihistamine, acetaminophen, and a corticosteroid prior to each infusion of pegloticase. To standardize this regimen, subjects will receive fexofenadine (180 mg orally) the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, immediately prior to each infusion.

The risk of anaphylaxis and IRs is higher in patients whose sUA level increases to >6 mg/dL. Beginning with Week 2, subjects with sUA level >6 mg/dL at 2 consecutive study visits will be classified as a non-responder. These subjects will discontinue from treatment but remain on study.

Refer to the current version of the FDA-approved KRYSTEXXA Full Prescribing Information and KRYSTEXXA Investigator's Brochure for detailed information concerning the safety profile of pegloticase.

### 7.1.3 Methotrexate Overview and Risks

MTX is a folic acid reductase inhibitor used as a disease-modifying, anti-rheumatic drug for the treatment of autoimmune diseases. Methotrexate is a drug well-known to rheumatologists, has a well-established and understood safety profile, and is known to prevent the formation of anti-drug antibodies (Strand et al., 2017).

Adverse events (AEs) that may be experienced by subjects treated with MTX include:

- Gastrointestinal: nausea, vomiting, diarrhea, stomatitis
- Hematologic and oncologic: leukopenia, thrombocytopenia
- Hepatic: hepatotoxicity, increased serum alkaline phosphatase, increased serum bilirubin, increased serum transaminases
- Infection: increased susceptibility to infection
- General: malaise, fatigue, dizziness, alopecia, photosensitivity

Additionally, MTX can cause fetal death or teratogenic effects. Pregnancy should be avoided if either partner is receiving MTX, during and for a minimum of three months after MTX therapy for the non-vasectomized male. For females of child bearing potential, pregnancy should be avoided for at least one ovulatory cycle after MTX therapy.

Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray.

Refer to the current version of the FDA-approved MTX Full Prescribing Information for detailed information concerning the safety profile of MTX.

## 7.2 Rationale for this Study

Immunogenicity (anti-pegloticase antibodies) in response to pegloticase therapy may lead to loss of therapeutic response and/or AEs, including IRs. In the phase 3 studies, IRs occurred more commonly in subjects whose sUA values increased above 6 mg/dL, after initially showing response following the first 1 or 2 infusions. The titer of the anti-drug antibody was also associated with loss of response, with subjects having the highest levels of anti-drug antibodies showing the lowest response rates.

The development of anti-drug antibodies can be influenced by drug and treatment-related factors, as well as patient characteristics. A potential prophylactic strategy to manage anti-drug antibody response with pegloticase is the co-administration of immunomodulatory therapy. Various methods are used to reduce antibody production in other settings, the most common of which is the use of traditional rheumatoid arthritis disease-modifying drugs, such as MTX, azathioprine,

mycophenolate mofetil, leflunamide, and others, as is commonly implemented with rheumatoid arthritis biological therapy (e.g., infliximab and other infusible and subcutaneous antibody products) [Strand et al, 2017].

MTX is the most commonly used non-biological disease modifying agent worldwide and is frequently used in combination with other biological therapies [Strand et al, 2017].

In the current study, MTX will be evaluated for its ability to improve the response rate and reduce IRs with pegloticase by reducing drug immunogenicity. Prospective use of sUA stopping rules, with pegloticase treatment cessation (but study continuation) when a subject has an sUA level > 6 mg/dL on two consecutive study visits, will also help confirm the value of this approach to reduce IR risk.

## 7.3 Rationale for Dose Selection

**Pegloticase dose selection**

The dose of pegloticase and instructions for use are consistent with the current pegloticase prescribing information. Refer to the current version of the FDA-approved KRYSTEXXA Full Prescribing Information.

**Methotrexate dose selection**

Methotrexate is among the most well-studied agents shown to reduce anti-drug antibodies in numerous trials (Strand et al., 2017). Methotrexate as monotherapy for RA and psoriatic arthritis is generally administered at doses of 7.5 to 15 mg/week, with doses titrated up as necessary and tolerated to 25-30 mg/week (Visser and van der Heijde, 2009; Mouterde et al., 2011; Ceponis and Kavanaugh, 2010; Mease 2013). These dose levels have generally been both effective and safe. A similar dose range of MTX has been used in combination with biologic DMARDs when the biologic DMARDs have been used as therapy for both rheumatoid and psoriatic arthritis, as well as other conditions (REMICADE Product Labeling, 2018; HUMIRA Product Labeling, 2018; CIMZIA Product Labeling, 2018). Importantly, the CONCERTO study (Burmester et al., 2014) demonstrated that doses of 10-20 mg/week of MTX were more effective than lower doses of MTX in inhibiting induction of ADA to adalimumab. Finally, the dose of 15 mg/week of MTX in a large population of subjects with cardiovascular disease with co-morbidities has been shown to be safe. For these reasons, a dose of MTX of 15 mg/week was selected for co-administration with pegloticase in the MIRROR pivotal study.

Bressolle et al. (1998) have shown that in RA patients, the half-life of MTX is doubled when the creatinine clearance decreases to <45 mL/min. The Methotrexate Product Labeling (2018) states, “Renal excretion occurs by glomerular filtration and active tubular secretion” and “Excellent correlation has been reported between MTX clearance and endogenous creatinine clearance.” The labeling also indicates that the dose of MTX should be reduced in patients who have renal impairment. The 2008 ACR recommendations for use of MTX (Saag et al, 2008) indicate that MTX is contraindicated when the estimated creatinine clearance is <30 mL/min. Based on this

literature, only subjects with an estimated glomerular filtration rate (eGFR) >40mL/min/1.73m2 will be eligible for enrollment.

# 8 STUDY OBJECTIVES

The overall objective of the double-blind portion of the study is to assess the potential for pegloticase with MTX to increase the response rate seen with pegloticase alone, and to characterize the safety, tolerability and pharmacokinetics (PK) of the concomitant use of pegloticase with MTX, by comparing pegloticase co-administered with MTX to pegloticase co-administered with placebo for MTX in adults with uncontrolled gout.

Primary Objective

The primary objective is to evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the response rate during Month 6 (Weeks 20, 21, 22, 23 and 24), as measured by the sustained normalization of serum uric acid (sUA) to <6 mg/dL for at least 80% of the time during Month 6.

Secondary Objectives (analyzed sequentially)

1. Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the response rate during Month 9 (Weeks 32, 34, and 36), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 9.
2. Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the response rate during Month 12 (Weeks 48, 50, and 52), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 12.
3. Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the complete resolution of ≥ 1 tophi (using digital photography) at Week 52 in subjects with tophi at baseline.

Exploratory Objectives

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in urate volume and bone erosions due to gout to Weeks 14, 24, and 52 based on DECT of the hands and feet.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in bone erosions due to gout to Weeks 24 and 52 based on X-rays of the hands and feet.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the complete resolution of ≥ 1 tophi (using digital photography) at Weeks 24 and 36 in subjects with tophi at baseline.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in tophus size (long axis measured using digital photography) to Weeks 14, 24, 36 and 52 in subjects with tophus present at baseline.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the response rate during Month 3 (Weeks 10, 12 and 14), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 3.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the overall response rate, as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 3 (Weeks 10, 12, and 14) and Month 6 (Weeks 20, 21, 22, 23, and 24) combined.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on reducing sUA to < 5 mg/dL for at least 80% of the time during Months 3, 6, 9 and 12, individually.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in sUA at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the time to first sUA > 6 mg/dL.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the time to two consecutive sUA > 6 mg/dL (sUA stopping rule).
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the percentage of non-hyperuricemic (sUA < 6 mg/dL) time during Months 3, 6, 9 and 12.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in HAQ Pain Score at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in HAQ Health Score at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase and MTX vs. pegloticase and placebo for MTX on the mean change from baseline in HAQ-DI Score at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in tender joint count (68-point scale) at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in swollen joint count (66-point scale) at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in number of tender or swollen joints at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in physician global assessment of gout at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the proportion of subjects whose treatment goals are met at Weeks 24 and 52.
- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in SBP and DBP to each visit.

- Assess the PK of pegloticase.
- Assess the incidence of anti-PEG and anti-Uricase IgG antibodies.

Safety and Tolerability Objectives

- AE/SAE profile overall for pegloticase and the combination of pegloticase and MTX
  - Incidence of AESI: IRs, anaphylaxis, gout flares, cardiovascular events
- Laboratory tests
- Vital signs and physical examination

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

This study is a Phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of pegloticase with MTX vs. pegloticase with placebo for MTX in adult subjects with uncontrolled gout.

The study design will include: 1) a Screening Period (screening should be completed within 4 weeks prior to Week -6); 2) a 2-week MTX Tolerability Assessment Period consisting of 2 weeks oral MTX for all subjects; 3) a Run-In Period consisting of randomization followed by 4 weeks of blinded oral MTX or placebo for MTX; 4) a 52-week Pegloticase + IMM Period; 5) a Safety Follow-up (Phone/Email/Site Visit) and 6) a 3 and 6 month Post Treatment Follow-up.

All subjects who meet eligibility criteria at Screening will begin 15 mg MTX orally weekly at the Week -6 visit. Subjects will also take folic acid 1 mg orally every day beginning during the MTX Tolerability Assessment Period (Week -6 to Week -4) and continuing until prior to the Week 52 Visit.

Subjects must be able to tolerate the weekly dose of MTX 15 mg for 2 weeks to be eligible to be randomized at Week -4. Subjects who are unable to tolerate the 15 mg dose of MTX during the 2 weeks preceding the Week -4 visit during the Run-in Period will be considered screen failures.

Subjects who tolerate the weekly 15 mg MTX dose during the 2 weeks preceding Week -4 Visit and continue to meet eligibility criteria will be randomized at the Week -4 Visit in a 2:1 ratio (stratified by presence of tophi) to receive either blinded oral 15 mg MTX or blinded oral placebo for MTX. Tophi presence (yes, no) will be based on presence of at least one tophus identified by the Investigator. Subjects will continue to take the blinded MTX or placebo for MTX from Week -4 to Day 1 (the Run-in period) at the 15 mg MTX or placebo for MTX dose. If a subject does not tolerate the 15 mg MTX or placebo for MTX dose after randomization at the Week -4 Visit and prior to Day 1, the MTX or placebo for MTX may be dose-reduced or discontinued based on pre-specified criteria and after discussion with the Sponsor medical monitor. The subject will be allowed to remain in the study. After Day 1, MTX or placebo for MTX may be re-initiated. The subject will be re-initiated to the same treatment they were randomized to at Week -4. The re-initiated MTX or placebo for MTX will remain blinded.

All subjects who complete the Run-In Period will receive the first pegloticase infusion on Day 1. All subsequent doses and study visits will be scheduled based on the Day 1 visit date.

It is required that before a subject begins the pegloticase + IMM Period, he or she has been taking at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤10 mg/day) for ≥1 week before the first dose of pegloticase and continues flare prophylaxis per American College of Rheumatology guidelines [Khanna D et al. 2012] for the greater of 1) 6 months, 2) 3 months after achieving target serum urate (sUA < 6 mg/dL) for patients with no tophi detected on physical exam, or 3) 6 months after achieving target serum urate (sUA < 5 mg/dL) for patients with one or more tophi detected on initial physical exam that have since resolved. For IR prophylaxis, fexofenadine (180 mg orally) will be taken the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, immediately prior to each infusion.

During the Pegloticase + IMM Period, pegloticase 8 mg will be administered intravenously (IV) every 2 weeks from Day 1 through the Week 50 Visit for a total of 26 infusions; pegloticase will be administered after all pre-dose study visit assessments have been completed at each visit. The date and start and stop time of infusion will be recorded. Serum uric acid stopping rules will be applied: subjects with sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue treatment, complete the End of Pegloticase Infusion Visit procedures within 2 weeks and continue the subject visits according to the protocol (without treatment).

During the Pegloticase + IMM Period, subjects will be instructed to take MTX or placebo for MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase infusion and one additional weekly dose after the last infusion for subjects who have not stopped pegloticase due to sUA stopping rules; however, if a subject does not do so, MTX or placebo for MTX must be taken ≥60 minutes prior to each pegloticase infusion.

After Day 1, if a subject becomes unable to tolerate MTX or placebo for MTX, the MTX or placebo for MTX dose may be reduced and/or discontinued based on pre-defined criteria, and the subject may remain in the study.

The Investigator will review the clinical status and individual subject treatment goals at Screening, Week 24, Week 52 and the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of study/Early Termination Visit.

After the Week 52 Visit (or End of Pegloticase Infusion Visit [if applicable]), subjects should resume regular care for gout per the judgment of the treating physician, including resumption of urate lowering therapy (ULT) upon pegloticase discontinuation, if appropriate. Subjects will have a 3 and 6 Month Follow-up visit to assess clinical status, including sUA levels.

Subjects who receive at least one dose of MTX or placebo for MTX and are females of childbearing potential will receive a safety follow-up phone call/e-mail approximately 30 days

after the last dose of MTX or placebo for MTX to verify at least one ovulatory cycle has occurred after the last dose of MTX or placebo for MTX. If the subject has not ovulated, a urine pregnancy test will be performed. Subjects who receive at least one dose of MTX or placebo for MTX and who are non-vasectomized males, will be asked, 3 months after MTX or placebo for MTX discontinuation, regarding partner pregnancy.

Samples for measurement of sUA levels, PK analysis of pegloticase, pegloticase immunogenicity and MTX Polyglutamate analysis will be collected at visits indicated in the Schedule for Assessments (Section 2.1).

Safety assessments, including monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations, and monitoring of hematology and blood chemistry, will be performed.

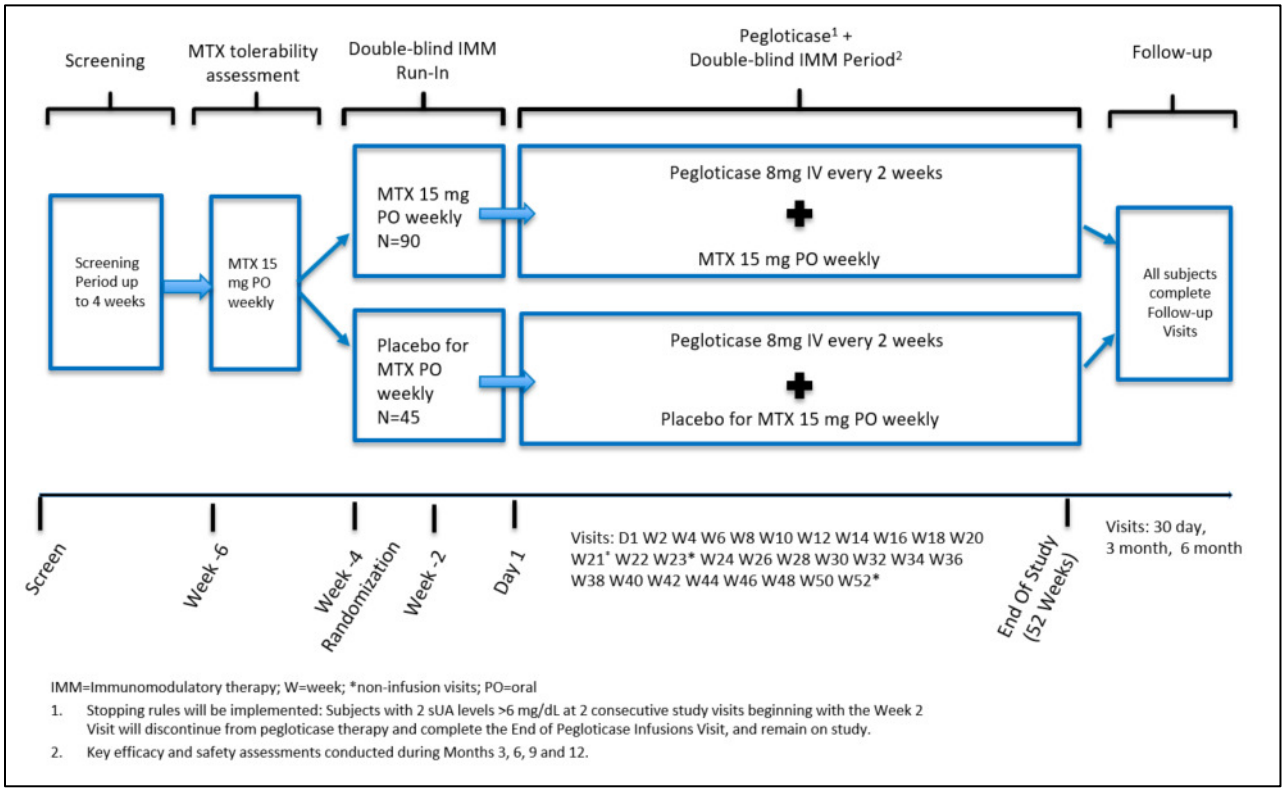
The total blood volume to be collected from each subject during this study is approximately 850 mL.

An external Data Monitoring Committee (DMC) will be convened to review data for safety and efficacy with timing and criteria outlined in the DMC Charter, with the possibility of DMC recommendation on study design modification per criteria also to be outlined in the Charter.

An independent external adjudication committee will review reported events of infusion reactions, cardiovascular events and anaphylaxis.

An overview of the study design is presented in the schematic below, and details of study activities are provided in Section 2.1.

## Figure 9.1 Schematic of Study Design



## 9.2 Discussion of Study Design

This study is a Phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of pegloticase in combination with MTX or pegloticase in combination with placebo for MTX in adult subjects with uncontrolled gout.

Immunogenicity (anti-pegloticase antibodies) in response to pegloticase therapy may lead to loss of therapeutic response and/or AEs, including IRs. A potential prophylactic strategy to manage anti-drug antibody response with pegloticase is the co-administration of immune-modulating therapy. MTX is the most commonly used non-biological disease modifying agent worldwide and is frequently used in combination with other biological therapies [Strand et al, 2017].

This study will include a 2-week MTX Tolerability Assessment Period, a 4-week Run-in Period including 4 weeks of blinded MTX or placebo for MTX, a 52-Week Pegloticase + IMM Period including MTX or placebo for MTX dosed weekly and 50 weeks of pegloticase infusion visits every 2 weeks and a Post Treatment Follow-up Period.

## 9.3 Selection of Study Population

### 9.3.1 Inclusion Criteria

Eligible subjects must meet/provide **all** of the following criteria:

1. Willing and able to give informed consent.
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.
3. Adult men or women ≥18 years of age.
4. Uncontrolled gout, defined as meeting the following criteria:
   - Hyperuricemia during the screening period defined as sUA ≥7 mg/dL, and;
   - Failure to maintain normalization of sUA with xanthine oxidase inhibitors at the maximum medically appropriate dose, or with a contraindication to xanthine oxidase inhibitor therapy based on medical record review or subject interview, and;
   - Symptoms of gout including at least 1 of the following:
     - Presence of at least one tophus
     - Recurrent flares defined as 2 or more flares in the past 12 months prior to screening
     - Presence of chronic gouty arthritis
5. Willing to discontinue any oral urate lowering therapy for at least 7 days prior to MTX dosing at Week -6 and remain off when receiving pegloticase infusions.
6. Women of childbearing potential (including those with an onset of menopause <2 years prior to screening, non-therapy-induced amenorrhea for <12 months prior to screening, or not surgically sterile [absence of ovaries and/or uterus]) must have negative serum/urine pregnancy tests during Screening and Week -6; subjects must agree to use 2 reliable forms of contraception during the study, one of which is recommended to be hormonal, such as an

oral contraceptive. Hormonal contraception must be started ≥1 full cycle prior to Week -6 (start of MTX) and continue for 30 days after the last dose of pegloticase, or at least one ovulatory cycle after the last dose of MTX or placebo for MTX (whichever is the longest duration after the last dose of pegloticase or MTX or placebo for MTX). Highly effective contraceptive methods (with a failure rate <1% per year), when used consistently and correctly, include implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or vasectomized partner.

7. Men who are not vasectomized must agree to use appropriate contraception so as to not impregnate a female partner of reproductive potential during the study, beginning with the initiation of MTX at Week -6 and continuing and for at least 3 months after the last dose of MTX or placebo for MTX.
8. Able to tolerate MTX 15 mg orally for 2 weeks (Week -6 through Week -4) prior to randomization.

### 9.3.2 Exclusion Criteria

Subjects will be ineligible for study participation if they meet **any** of the following criteria:

1. Weight >160 kg (352 pounds) at Screening.
2. Any serious acute bacterial infection, unless treated and completely resolved with antibiotics at least 2 weeks prior to the Week -6 Visit.
3. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis.
4. Current or chronic treatment with systemic immunosuppressive agents such as MTX, azathioprine, or mycophenolate mofetil; prednisone ≥10 mg/day or equivalent dose of other corticosteroid on a chronic basis (3 months or longer) would also meet exclusion criteria.
5. History of any transplant surgery requiring maintenance immunosuppressive therapy.
6. Known history of hepatitis B virus surface antigen positivity or hepatitis B DNA positivity.
7. Known history of hepatitis C virus RNA positivity.
8. Known history of Human Immunodeficiency Virus (HIV) positivity.
9. Glucose-6-phosphate dehydrogenase deficiency (tested at the Screening Visit).
10. Chronic renal impairment defined as estimated glomerular filtration rate (eGFR) <40 mL/min/1.73 $m^2$ or currently on dialysis.
11. Non-compensated congestive heart failure or hospitalization for congestive heart failure within 3 months of the Screening Visit, uncontrolled arrhythmia, treatment for acute

coronary syndrome (myocardial infarction or unstable angina), or uncontrolled blood pressure (>160/100 mmHg) prior to Randomization at Week -4.

12. Pregnant, planning to become pregnant, breastfeeding, planning to impregnate female partner, or not on an effective form of birth control, as determined by the Investigator.
13. Prior treatment with pegloticase, another recombinant uricase (rasburicase), or concomitant therapy with a polyethylene glycol-conjugated drug.
14. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product.
15. Contraindication to MTX treatment or MTX treatment considered inappropriate.
16. Known intolerance to MTX.
17. Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to MTX administration at Week -6 or plans to take an investigational drug during the study.
18. Liver transaminase levels (AST or ALT) > upper limit of normal (ULN) or albumin < the lower limit of normal (LLN) at the Screening Visit).
19. Chronic liver disease.
20. White blood cell count < 4,000/ul, hematocrit < 32 percent, or platelet count <75,000/ul.
21. Currently receiving systemic or radiologic treatment for ongoing cancer.
22. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix.
23. Diagnosis of osteomyelitis.
24. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
25. Unsuitable candidate for the study, based on the opinion of the Investigator (e.g., cognitive impairment), such that participation might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements or complete the study.
26. Alcohol use in excess of 3 alcoholic beverages per week.
27. A known intolerance to at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤10 mg/day).
28. Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest X-ray may be performed during Screening.

### 9.3.3 Removal of Subjects From Therapy or Study

All subjects are free to withdraw from study participation at any time, for any reason, and without prejudice to their further medical care. In addition, the Investigator may terminate a subject from the study at any time. However, subjects who are removed from pegloticase therapy should remain on study barring withdrawal of consent for study participation.

#### 9.3.3.1 Removal of Subjects From Pegloticase Therapy

In addition to completion of therapy through Week 52, the reason for discontinuation from the therapy should be recorded on the eCRF using 1 of the following categories:

- Lack of Efficacy. (i.e., sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit).
- Adverse Event. The subject experiences an AE that imposes an unacceptable risk to the subject's health (e.g., anaphylactic reaction), or the subject is unwilling to continue therapy because of an AE. Subjects who discontinue due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for the event is obtained.
- The Investigator has determined that pegloticase administration poses an unacceptable risk to the subject (specify reason).
- Subject refusal of additional therapy (specify reason).
- Study Terminated by Sponsor. The Sponsor, IRB, or regulatory agency terminates the study.
- Pregnancy
- Death

#### 9.3.3.1.1 Study considerations for subjects ending pegloticase infusions prior to 52 weeks

- Methotrexate/placebo for MTX, along with folic acid, will be discontinued at the time of cessation of pegloticase infusions prior to Week 52.
- All subjects will complete the End of Pegloticase Infusions Visit and will remain on study through Week 52 regardless of whether they stop infusions due to sUA stopping rules or other reason (e.g. withdrawal of consent for pegloticase infusions).
- Subjects are encouraged to continue to participate in all visits through the end of the study. Subjects are especially encouraged to complete study visits at the study site during key efficacy and safety collections at Weeks 20, 21, 22, 23, 24, 32, 34, 36, 48, 50 and 52, so that sUA labs and other key assessments can be completed. During visits between these key efficacy and safety collection visits, in subjects who have stopped infusions, subjects may complete study visits in person or via telephone to collect AEs, conmeds and gout flare information.
- Activities related to pre/post infusion monitoring or medication dispensation will not be completed once a subject has stopped pegloticase infusions. These activities include:
    - MTX/placebo for MTX compliance/reconciliation
    - Infusion reaction prophylaxis
    - IR prophylaxis compliance
    - Folic acid compliance
    - Pegloticase infusion
    - Pegloticase PK sampling
    - Pre-infusion MTX Polyglutamate sampling
    - MTX drug/dispensation related items

Post Treatment Follow-up:

The intent is to obtain at least 6 months of follow-up on each subject after cessation of pegloticase infusions. If these 6 months occur prior to end of study at Week 52, such as in the case of a subject who ends pegloticase infusions on or before Week 24, there will be no follow-up visits after the

Week 52/End of Study Visit. For subjects who end pegloticase infusions between Weeks 26 and 36, there will be at least 3 months of follow-up while the subject remains on-study prior to Week 52, and then one follow-up visit after the Week 52/End of Study Visit. For subjects who end pegloticase infusions between Weeks 38 and 52, there will be two follow-up visits at intervals of 3 months apart after the Week 52/End of Study Visit.

#### 9.3.3.2 Removal of Subjects From Study

In addition to completion of therapy and designated study visits through Week 52, the reason for discontinuation from the study should be recorded on the eCRF using 1 of the following categories:

- Lost to Follow-up. The subject does not return to the clinic for scheduled assessments, and does not respond to the site's attempts to contact the subject.
- Withdrawal of Consent. The subject withdraws from the study. The clinical site should attempt to determine the underlying reason for the withdrawal and document it on the eCRF; (i.e. AE, voluntary withdraw) Specify.
- Study Terminated by Sponsor. The Sponsor, IRB, or regulatory agency terminates the study.
- Death

### 9.3.4 Replacement Policy

#### 9.3.4.1 Subjects

No subject prematurely discontinued from the study for any reason will be replaced.

#### 9.3.4.2 Centers

A center may be closed and/or replaced for the following administrative reasons:

- Excessively slow recruitment.
- Poor protocol adherence.

#### 9.3.4.3 Screen Failures

Subjects who do not meet all of the inclusion criteria or meet any of the exclusion criteria between Screening and randomization at Week -4 will be considered screen failures. Subjects who do not meet all of the inclusion criteria or meet any of the exclusion criteria will be considered screen failures. Screen failures may be allowed to rescreen for the study if both the Investigator and Sponsor are in agreement regarding rescreening and if the Investigator determines that they can satisfy all of the eligibility criteria.

## 9.4 Treatments

### 9.4.1 Treatments Administered

During the MTX Tolerability Assessment Period (Week -6 until the Week -4 visit), all subjects will take MTX 15 mg orally weekly.

At the Week -4 visit, subjects who tolerated MTX will be randomized to receive MTX 15 mg or placebo for MTX orally weekly. Subjects will take the blinded MTX or placebo for MTX during the Run-in Period (from Week -4 to Day 1) at the 15 mg MTX dose or placebo for MTX dose.

During the Pegloticase + IMM Period, all subjects will receive pegloticase at a dose of 8 mg administered IV every 2 weeks for a total of 26 infusions from Day 1 through the Week 50 Visit. Subjects will continue taking MTX or placebo for MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase infusion and one additional weekly dose after the last infusion for subjects who have not stopped pegloticase due to sUA stopping rules.

After the Week 52 Visit (or End of Pegloticase Infusion Visit [if applicable]), subjects should resume regular care for gout per the judgment of the treating physician, including resumption of ULT upon pegloticase discontinuation, if appropriate. Subjects will have a 3 and 6 Month Follow-up visit to assess clinical status, including sUA levels.

#### 9.4.1.1 Folic Acid

Subjects will take folic acid 1 mg orally every day beginning at Week -6 (the start of MTX) until prior to the Week 52 Visit.

If the subject discontinues pegloticase due to the stopping rules or other reason, MTX/placebo for MTX should also be discontinued; as such, the subject will discontinue folic acid as well.

Prescriptions are to be filled at a local pharmacy, as needed. At study visits, the subject will be asked a Yes/No question whether folic acid was taken per protocol.

#### 9.4.1.2 Gout Flare Prophylaxis

It is required that before a subject begins the pegloticase + IMM Period, he or she has been taking at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤10 mg/day) for ≥1 week before the first dose of pegloticase and continues flare prophylaxis per American College of Rheumatology guidelines [Khanna D et al. 2012] for the greater of 1) 6 months, 2) 3 months after achieving target serum urate (sUA < 6 mg/dL) for patients with no tophi detected on physical exam, or 3) 6 months after achieving target serum urate (sUA < 5 mg/dL) for patients with one or more tophi detected on initial physical exam that have since resolved.

Prescriptions are to be filled at a local pharmacy, as needed. At study visits, the subject will be asked a Yes/No question whether gout flare prophylaxis was taken per protocol.

#### 9.4.1.3 Infusion Reaction Prophylaxis

Since IRs can occur with pegloticase, all subjects will receive IR prophylaxis prior to each infusion, consisting of an antihistamine, acetaminophen, and a corticosteroid. To standardize this regimen, subjects will receive fexofenadine (180 mg orally) the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, immediately prior to each infusion. Substitution of the corticosteroid is not allowed. The name,

dose, route, date, and time of administration of each prophylactic medication will be recorded in the medical record and in the eCRF. The Solumedrol used for IR prophylaxis will be supplied by the site. Other IR medications administered prior to each infusion may also be supplied by the site.

Prescriptions are to be filled at a local pharmacy, as needed. At study visits, the subject will be asked a Yes/No question whether IR prophylaxis was taken per protocol.

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 trained in managing IRs and, in the use of the emergency equipment will be readily available during, and for 1 hour after, the infusion. As IRs can occur after the completion of the infusion, subjects will be observed for 1 hour post-infusion.

### 9.4.2 Identity of Investigational Products

#### 9.4.2.1 Pegloticase

Pegloticase is a clear, colorless, sterile solution in phosphate-buffered saline intended for IV infusion after dilution. 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 dihydrate, and water for injection.

#### 9.4.2.2 Methotrexate and Placebo for Methotrexate

MTX 2.5 mg tablets for oral administration during the MTX Tolerability Assessment Period (Week -6 through Week -4) will be provided to subjects as a commercially available generic.

MTX 2.5 mg tablets for oral administration during the Run-In Period (Week -4 through Day 1) and the Pegloticase + IMM Period (Day 1 through Week 52) will be provided to subjects as a methotrexate 2.5 mg tablet over-encapsulated in a size zero Swedish Orange capsule.

Placebo for methotrexate 2.5 mg for oral administration during the Run-In Period (Week -4 through Day 1) and the Pegloticase + IMM Period (Day 1 through Week 52) will be provided as a size zero Swedish Orange capsule with Avicel® filling.

A dosing calendar will be provided to subjects at the Week -6 Visit to record each dose of MTX or placebo for MTX and the date and time of each dose on each calendar day of MTX or placebo for MTX administration.

See MTX Full Prescribing Information for additional detail.

### 9.4.3 Labeling

Pegloticase (KRYSTEXXA) is commercially available in the United States and will be supplied by PCI Pharma Services packaged in sterile, single-use 2-mL glass vials with a Teflon®-coated (latex-free) rubber injection stopper to deliver pegloticase as 8 mg of uricase protein in 1 mL volume. An ancillary label will be fixed to the vial and carton that identifies the study, allows

subject information to be entered, and contains the investigational use caution statement according to the FDA Title 21 CFR Part 312 requirements. Each vial label will have a unique number.

MTX for use during the MTX Tolerability Assessment will be provided to sites by PCI Pharma Services as tablets in bottles. An ancillary label will be fixed to the bottle that identifies the study, allows subject information to be entered, and contains the investigational use caution statement according to the FDA Title 21 CFR Part 312 requirements. Each bottle and carton (if applicable) label will have a unique number. Bottles will be provided to study subjects at the Week -6 Visit for weekly dosing after visit procedures and inclusion/exclusion criteria are confirmed.

Over-encapsulated MTX or placebo for MTX for use during the Run-in and Pegloticase + IMM Period will be provided to sites by PCI Pharma Services as capsules in bottles. A clinical label will be fixed to the bottle that identifies the study, allows subject information to be entered, and contains the investigational use caution statement according to the FDA Title 21 CFR Part 312 requirements. Each bottle label will have a unique number. Bottles will be provided to study subjects after the Week -4 Visit for weekly dosing after visit procedures and randomization are confirmed.

### 9.4.4 Storage

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. Pegloticase diluted in infusion bags is stable for 4 hours at 2°C to 8°C (36°F to 46°F) and for 4 hours at room temperature (20°C to 25°C, 68°F to 77°F).

MTX tablets and capsules and placebo for MTX capsules will be stored between 20°C to 25°C (68°F to 77°F) and protected from light.

### 9.4.5 Drug Accountability

Clinical supplies will be dispensed only in accordance with the protocol. Accurate records of the clinical supplies received, the amount dispensed for each subject, and the amount remaining at the conclusion of the study will be maintained. Each study site will also maintain individual subject drug logs/electronic logs to account for MTX tablets (dispensed for the MTX Tolerability Assessment Period) and MTX or placebo for MTX capsules (dispensed for the Run-in and Pegloticase + IMM Period) and subject compliance will be monitored by the site at each visit (see Section 9.4.11).

Subjects will bring the MTX or placebo for MTX dosing calendar to each study visit for assessment of compliance. Subjects will bring the MTX or placebo for MTX bottle to each visit for a compliance check by the site. The site will manually count the tablets/capsules and re-dispense the bottle to the subject. At the end of the study or if the subject prematurely discontinues the study, the subjects will return any unused or partially used study drugs to the site.

Investigational clinical supplies will be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated assistants have access.

Please reference the Study Pharmacy Manual for more detailed information on MTX, placebo for MTX and pegloticase packaging, labeling, storage, and destruction.

### 9.4.6 Study Drug Administration and Timing of Dose for each Subject

#### 9.4.6.1 Description of Clinical Supplies

PCI Pharma Services will supply study drugs (pegloticase, MTX and placebo for MTX) to clinical sites. Ancillary supplies for dosing will be provided by the study site (i.e., infusion bags containing saline, syringes, needles, alcohol swabs, gauze pads, bandages, and biohazard containers for safe storage of used needles and syringes).

#### 9.4.6.2 Determination of Dose Volume

Pegloticase will be administered as an admixture of 8 mg in 250 mL of 0.45% or 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) for IV infusion.

In the event of an IR, the infusion should be slowed, or stopped, and restarted at a slower rate at the discretion of the Investigator. Infusions subsequent to an IR in an individual subject may be given in a larger volume of diluent, not to exceed 500 mL. In this case, the infusion duration will also be extended to a minimum of 3 hours.

#### 9.4.6.3 Details Concerning Timing and Dose Administration

##### 9.4.6.3.1 Preparation and Administration

###### 9.4.6.3.1.1 Preparation

Vials of pegloticase 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, 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. In accordance with good pharmacy practice, gloves will be worn during preparation of the dose.

Pegloticase must be started within 4 hours of dilution. Before administration, the diluted solution of pegloticase will be allowed to reach room temperature. Pegloticase must never be subjected to artificial heating.

###### 9.4.6.3.1.2 Dose and Administration

**Methotrexate**

During the MTX Tolerability Assessment Period (Week -6 until the Week -4 visit), all subjects will take MTX 15 mg orally weekly.

At the Week -4 visit, subjects who tolerated methotrexate will be randomized to receive MTX 15 mg or placebo for MTX orally weekly. Subjects will be blinded to MTX or placebo for MTX beginning at Week -4 through the remainder of the study. Subjects will continue to take the blinded MTX or placebo for MTX during the Run-in Period (from Week -4 to Day 1) at the 15 mg MTX dose or placebo for MTX dose. Investigators may choose to have subjects take the weekly dose divided over the day (i.e. BID, TID). If a subject does not tolerate the 15 mg MTX or placebo for MTX dose after randomization at the Week -4 Visit and prior to Day 1, the MTX or placebo for MTX may be dose-reduced or discontinued based on pre-specified criteria and after discussion with the Sponsor medical monitor. The subject will be allowed to remain in the study. After Day 1, MTX or placebo for MTX may be re-initiated. The subject will be re-initiated to the same treatment they were randomized to at Week -4, however the dose may be adjusted (See Section 9.4.6.3.2.2). The re-initiated MTX or placebo for MTX will remain blinded to the subject. During the Run-in Period, if a dose is missed, it should be taken as soon as it is remembered. If it is within 48 hours of the next scheduled dose, the subject will be instructed to skip the missed dose and resume at the next regularly scheduled time; thus, subjects will be instructed not to double a dose to make up for a missed dose if within 48 hours of the next dose.

During the Pegloticase + IMM Period, subjects will be instructed to take MTX or placebo for MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase infusion and one additional weekly dose after the last infusion for subjects who have not stopped pegloticase due to sUA stopping rules; however, if a subject does not do so, MTX or placebo for MTX must be taken ≥60 minutes prior to each pegloticase infusion. Investigators may choose to have subjects take the weekly dose divided over the day (i.e. BID, TID). The total MTX or placebo for MTX dose should be taken within 24 hours, preferably the same calendar day each week, with the date and time of each dose recorded in the dosing calendar. If a subject becomes unable to tolerate the MTX or placebo for MTX during the Pegloticase + IMM Period, the dosage may be decreased.

Refer to Section 9.4.12 for contraception requirements.

Subjects will take folic acid 1 mg orally every day beginning at Week -6 (the start of MTX) until prior to the Week 52 Visit.

**Pegloticase**

All subjects will receive pegloticase at the same dose of 8 mg administered IV every 2 weeks for a total of 12 infusions from Day 1 through the Week 50 Visit for a total of 26 infusions (Pegloticase + IMM Period). Subjects will not be fasting on the day of infusion and will be encouraged to have a snack or normal meal before or after the infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion (see Section 9.5.1.1).

Standardized IR prophylaxis consisting of pre-treatment with antihistamines, acetaminophen, and corticosteroids will accompany each infusion (see Section 9.4.1.3). The drug name, dose, and timing of these prophylactic medications will be recorded.

Pegloticase will be administered as an admixture of 8 mg in 250 mL of 0.45% or 0.9% Sodium Chloride Injection, USP for IV infusion by gravity feed or infusion pump. Pegloticase will not be administered as an IV push or bolus.

In a patent IV site, using tubing with no in-line filter, the pegloticase preparation will be infused over approximately 120 ±15 minutes while the subject is under close observation for any signs of distress. If an in-line filter is used, it should be 0.2 µm or larger. At the end of the infusion, the IV line will be flushed with 10 mL of normal saline to ensure the full dose is administered. The date and time of infusion start and stop (inclusive of the IV flush) will be recorded.

#### 9.4.6.3.2 Dose Modifications, Interruptions, and Delays

##### 9.4.6.3.2.1 Pegloticase Modifications

Infusion of pegloticase will be immediately held if the subject experiences any significant IR such as respiratory distress, agitation, chest or back pain, urticaria, or another clinically significant event occurring during infusion. If the AE meets the definition of an SAE for IR, the infusion should not be restarted unless the site Investigator determines it is safe to resume the infusion. If the AE does not meet the definition of an SAE for IR, the site Investigator may make the decision to re-start the infusion depending upon the nature and severity of the AE.

Infusions subsequent to an IR in an individual subject may be given in a larger volume of diluent, not to exceed 500 mL. In this 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 eCRF.

##### 9.4.6.3.2.2 MTX/Placebo for MTX Dose Titration Algorithm and Intolerance Criteria

During the MTX Tolerability Assessment Period subjects will be considered a screen failure if any of the following new laboratory findings or symptoms reflecting MTX intolerance occur:

1. Abnormal Hematology findings:
    a. WBC < 3.5 x $10^9$/L
    b. Platelets < 75 x $10^9$/L
    c. Hematocrit < 32%
2. Abnormal hepatic function findings:
    a. AST/ALT >1.5 x upper limit of reference range and
    b. Albumin < lower limit of reference range
3. Abnormal renal function: eGFR <40ml/min/1.73 $m^2$ (as estimated with the MDRD equation).
4. New clinically important signs and symptoms, such as the following:
    a. Rash or oral ulceration
    b. Persistent nausea, vomiting and diarrhea
    c. New or increasing dyspnea or dry cough, or unexplained cough with fever
    d. Severe sore throat, abnormal bruising
    e. Severe headaches, fatigue, and problems concentrating

Note that if minor clinical symptoms emerge, such as mild stomatitis, mild GI discomfort, etc., the investigator may increase folic acid dose (e.g. 2 mg daily) or recommend a divided dose of MTX (e.g. 3 tabs of 2.5 mg in the morning and evening on the day of dosing); if symptoms improve, the subject will not be considered a screen failure on the basis of that symptom.

During the Run-In and Pegloticase+IMM Period, MTX or placebo for MTX dose guidance based on new laboratory findings or new symptoms is as follows:

| Lab Parameters | Value | MTX or placebo for MTX Dose Change |
|---|---|---|
| WBC | $3.0 \times 10^9$/L ~ $3.5 \times 10^9$/L | Decrease to 10 mg |
| | < $3.0 \times 10^9$/L | Temporary stop |
| Platelets | < $50 \times 10^9$/L | Temporary stop |
| Hematocrit | < 27% | Temporary stop |
| AST/ALT | Between 1.5 ~ 2 x ULN | Decrease to 10 mg |
| | > 2 x ULN | Temporary stop |
| eGFR | < 30 ml/min/1.73 $m^2$ | Temporary stop |
| New clinically important symptoms/signs* | Yes | Temporary stop |

* New clinically important symptoms or important medical events:

a. Rash or oral ulceration
b. Persistent nausea, vomiting and diarrhea
c. New or increasing dyspnea or dry cough, or unexplained cough with fever
d. Severe sore throat, abnormal bruising
e. Severe headaches, fatigue, and problems concentrating
f. Any other important medical events that might increase methotrexate toxicity or pre-dispose to new or worsening infection (e.g. undergoing surgery, hospitalization, being treated with antibiotics, having a clinical infection, developing new clinically significant pericardial / pleural effusion or ascites)

Note that if minor clinical symptoms emerge, such as mild stomatitis, mild GI discomfort, etc., the investigator may increase folic acid dose to 2 mg daily or recommend a divided dose of MTX or placebo for MTX (e.g. 3 tabs of 2.5 mg in the morning and evening on the day of dosing) and monitor for symptom resolution.

Investigators should discuss the emergence of any one of the following criteria with the medical monitor to review the case:

1. ALT/AST > 1.5 x ULN on 3 of any 5 consecutive measures
2. Albumin < 0.8 x LLN on 2 consecutive measures
3. Any laboratory or clinical symptoms leading to temporary stop on 3 consecutive measures, in which case the medical monitor will review to consider re-initiation, a continued temporary stop, or a permanent stop in discussion with the PI.

Guidance for increasing MTX or placebo for MTX back towards 15 mg after dose reduction, based on improvement or resolution of abnormal liver enzymes (>2 × upper limit of normal):

1. When liver enzymes return to values ≤1.5 × upper limit of normal, increase MTX or placebo for MTX dose by 2.5 mg and reassess in 2 weeks.
2. If liver enzymes remain ≤1.5 × upper limit of normal, increase MTX or placebo for MTX dose by 2.5 mg and reassess in 2 weeks.

Improvement of other laboratory abnormalities potentially attributed to MTX or placebo for MTX may also warrant titration back up to 15 mg weekly, based on PI judgement and in discussion with the Sponsor medical monitor.

#### 9.4.6.3.2.3 Gout Flare Treatment

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including pegloticase. Subjects will be instructed to contact the site within 12 hours of the onset of symptoms. Gout flares will be confirmed through questioning or direct observation, as detailed in Section 9.5.4.8. All subjects who experience a gout flare during the study will be prescribed anti-inflammatory treatment (e.g., NSAID, colchicine, corticosteroids and intra-articular steroid injections), as is clinically indicated or deemed necessary on an individual basis at the discretion of the investigator. Pain medications for gout flare should be administered according to standard of care as is clinically indicated or deemed necessary on an individual basis at the discretion of the investigator. All medications should be documented on the concomitant medication eCRF.

Colchicine will be prescribed in a medically appropriate dose range of 0.6 to 1.8 mg/day, usually dosed as 0.6 mg orally twice per day unless reduced dosing is necessitated by renal insufficiency or gastrointestinal intolerance. The precise dose and regimen of colchicine will be individualized for each subject by the Investigators and documented on the concomitant medication eCRF.

#### 9.4.6.3.2.4 Infusion Reaction Treatment

Subjects must be monitored closely for signs and symptoms of IRs. In the event of an IR, the infusion should be slowed, or stopped, and restarted at a slower rate at the discretion of the Investigator. If a serious IR occurs, the infusion should be discontinued and treatment should be provided, as needed.

If a subject experiences an AE suspected to be an IR:

- A physical examination will be performed to capture medically relevant details, including, but not limited to, a thorough dermatologic examination for detection of erythema, urticaria (hives), or peri-oral or lingual edema; a chest examination for breath sounds, stridor or wheezing; and a cardiac examination with attention to irregular heartbeat.
- Vital signs (sitting or supine blood pressure, heart rate, respiratory rate, and body temperature) will be captured at least every 30 minutes until the resolution or stabilization of the AE.
- A serum sample will be collected in a serum-separating tube at that time or at the subsequent visit. The sample will be centrifuged, frozen at -20°C or colder, and stored for the batch shipment to a Horizon designated laboratory for evaluation of pegloticase antibodies at a future date.

If, in the Investigator's opinion, the subject is experiencing an anaphylactic reaction (see Section 9.5.4.1.1.5), pegloticase should be immediately discontinued. Any incidence of anaphylaxis should be reported as an SAE.

The Investigator may administer any medically indicated pharmacologic agent or procedure intended to relieve symptoms (CAUTION: no other drugs can be mixed in the pegloticase infusion bag). Signs and symptoms of the AE and drugs given for treatment are to be recorded in the medical record and in the eCRF.

After the first incidence of an IR that does not meet the criteria of anaphylaxis (see Section 9.5.4.1.1.5) or does not meet serious criteria, the Investigator may elect to initiate the next infusion at a slower rate. Additionally, the Investigator may choose to prescribe 20 mg prednisone to be taken in the morning of the next infusion. All changes to infusion rate or dilution, and drugs given for prophylaxis or treatment, are to be recorded in the medical record and in the eCRF.

### 9.4.7 Method of Assigning Subjects to Treatment Groups

Medidata Randomization and Trial Supply Management (RTSM) will be used to randomly assign subjects in a ratio of 2:1 (stratified by presence of tophi) to receive MTX in combination with pegloticase or placebo for MTX in combination with pegloticase.

Specific procedures for randomization through Medidata are contained in the study procedures manual.

### 9.4.8 Blinding

<u>Pegloticase</u>

Because all subjects will receive pegloticase, this study drug will be administered without blinding to pegloticase administration, and all subjects, investigators and site personnel will know that all subjects are receiving pegloticase.

<u>Methotrexate</u>

The Sponsor, Investigator, study site personnel and study subject will remain blinded to each subject's treatment assignment (MTX or placebo for MTX). RTSM will provide access to blinded subject treatment information during the study in the case of medical emergency. The study blind should be broken only if the safety of a subject is at risk and the treatment plan depends on which medication (MTX or placebo for MTX) he or she received. Unless the subject is at immediate risk, the Investigator must make diligent attempts to contact the Sponsor or Sponsor's designee before unblinding the subject's data. If a subject's data are unblinded without prior knowledge of the Sponsor, the Investigator must notify the Sponsor as soon as possible and no later than the next business day. All circumstances surrounding the event must be clearly documented.

The Sponsor's Pharmacovigilance department or designee will unblind the identity of the study medication for an unexpected, drug-related SAE (related to MTX or placebo for MTX only) for submission to health authorities and IRB/IEC according to applicable regulatory requirements. However, the results will not be shared with other Sponsor representatives or staff at study sites. Details of subjects who are unblinded during the study will be included in the Clinical Study Report.

Unblinding for independent pharmacological analysis of biological samples or SAE reporting will be performed according to procedures in place to ensure integrity of the data.

The date and the reason that the blind was broken must be recorded in the eCRF.

Unblinding of Data for the Data Monitoring Committee (DMC)

The external DMC will oversee and interpret the interim analysis safety and efficacy data per a pre-defined charter. The external statistical center will provide unblinded data for the DMC review.

All investigative site staff directly involved in this study will remain blinded from randomization through analysis of the final data and all site close-out visits, except for emergency unblinding as described in Section 9.4.8. The Sponsor and its designees will remain blinded until after the database lock for the primary analysis unless directed otherwise by the DMC.

### 9.4.9 Prior and Concomitant Therapy

Medication history (i.e., prior medications) will include all prior gout medications, starting at the time of diagnosis and up to the Screening Visit, and all other medications taken from 1 year prior to the Screening Visit.

Concomitant medications are defined as drug or biological products other than the study drugs (or prior gout medications) taken by a subject from Screening through the Post Treatment Follow-up Visits. This includes other prescription medications (including preventive vaccines), over the counter medications, herbal medications, vitamins, and food supplements.

Information about prior and concomitant medications, including those used for any duration to treat an AE, will be collected on source documents and the appropriate eCRFs at each visit. The generic

name of the medication, indication, dose, unit, frequency, route of administration, and start and stop dates will be recorded.

Subjects will be directed to discontinue current urate-lowering therapy prior to initiation of pegloticase therapy as per the current package insert. Other medications used at the time of study initiation may be continued at the discretion of the Investigator.

### 9.4.10 Restricted Medications

Subjects should not receive the following medications from the time of Screening through the end of pegloticase and MTX or placebo for MTX treatment:

- Oral urate-lowering therapies including allopurinol, febuxostat, probenecid, lesinurad, or other ULT for gout.
- Any PEG-conjugated drug
- Any other investigational agent
- Any Methotrexate other than the study approved investigational product, azathioprine, mycophenolate mofetil, or other systemic immunosuppressants aside from glucocorticoids for gout flare prophylaxis (≤ 10 mg prednisone or equivalent per day) or intermittent gout flare treatment
- If a subject is treated with antibiotics, refer to Section 9.4.6.3.2.2.

### 9.4.11 Treatment Compliance

A dosing calendar will be provided to subjects at the Week -6 Visit for recording the dose/s of MTX/placebo for MTX and the date and time of each dose on each calendar day of MTX/placebo for MTX administration. The dosing calendar and bottle of MTX/placebo for MTX should be brought to each study visit for assessment of compliance. Adherence to the MTX/placebo for MTX regimen will also be recorded by the study coordinator at study visits in the eCRF by recording the date of each MTX/placebo for MTX dose (mg), frequency and time of each dose per calendar day. Subjects who have taken at least 80% of the protocol-specified amount of MTX/placebo for MTX will be considered compliant. Noncompliant subjects will be re-educated on compliance.

At study visits, the subject will be asked a Yes/No question whether folic acid, gout flare, and IR prophylaxis were administered.

Pegloticase will be administered at the study site by trained personnel. The date and time of infusion start and stop (inclusive of the 10-mL flush) will be recorded.

### 9.4.12 Contraception Requirements

Women of childbearing potential (including those with an onset of menopause <2 years prior to screening, non-therapy-induced amenorrhea for <12 months prior to screening, or not surgically sterile [absence of ovaries and/or uterus]) must agree to use 2 reliable forms of contraception during the study, one of which is recommended to be hormonal, such as an oral contraceptive.

Hormonal contraception must be started ≥1 full cycle prior to Week -6 (start of MTX) and continue for 30 days after the last dose of pegloticase, or at least one ovulatory cycle after the last dose of MTX or placebo for MTX (whichever is the longest duration after the last dose of pegloticase or MTX or placebo for MTX). Highly effective contraceptive methods (with a failure rate <1% per year), when used consistently and correctly, include implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or vasectomized partner

Men who are not vasectomized must agree to use appropriate contraception so as to not impregnate their female partner during the study and for at least 3 months after the last dose of MTX or placebo for MTX. Men must agree to use appropriate contraception from Week -6 through 3 months post the last dose of MTX or placebo for MTX. Appropriate contraception methods include condom use and abstinence.

## 9.5 Efficacy, Quality-of-Life, Pharmacokinetic, and Safety Variables

The Schedule of Assessments is provided in Section 2.1.

### 9.5.1 Efficacy Variables

Efficacy will be assessed based on measurement of sUA levels, tophus resolution, tophus size, tender and swollen joint counts, patient and physician global assessments of gout, joint pain, and DECT and X-ray of hands and feet.

#### 9.5.1.1 Serum Uric Acid

Serum samples for measurement of sUA levels will be collected at the Screening Visit, the Week -6 Visit (prior to the first dose of MTX), the Week -4 Visit (Randomization) and the Week -2 Visit during the Run-in Period; within 48 hours prior to each pegloticase infusion and after the end of each pegloticase infusion prior to discharge from the site during the Pegloticase + IMM Period on Day 1, at the Weeks 2, 6, 10, 12, 14, 20, 22, 24, 32, 34, 36, 48 and 50; within 48 hours prior to each pegloticase infusion at Weeks 4, 8, 16, 18, 26, 28, 30, 38, 40, 42, 44 and 46. Additional serum samples for sUA levels will be collected at non-infusion Visits at Weeks 21 and 23 and the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of study/Early Termination Visit and 3 and 6 month Follow-up Visits. Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue pegloticase and complete the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of study/Early Termination Visit procedures.

Two separate samples/tubes of blood should be collected within 48 hours prior to the pegloticase infusion (except on Day 1 when only 1 pre-infusion sample is required for the central laboratory). One sample/tube will be assessed by the site's local laboratory to be used for on-study subject management; pre-infusion sUA results must be reported by the local or central laboratory prior to each pegloticase infusion. If a local laboratory sample is drawn (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit. The second sample/tube will be sent to the central laboratory for analysis and recording in the database. See the Laboratory Manual for instructions for alternate scenarios.

A subject with an sUA level >6 mg/dL (based on the local or central laboratory) at 2 consecutive study visits, beginning with the Week 2 Visit, will be discontinued from pegloticase treatment.

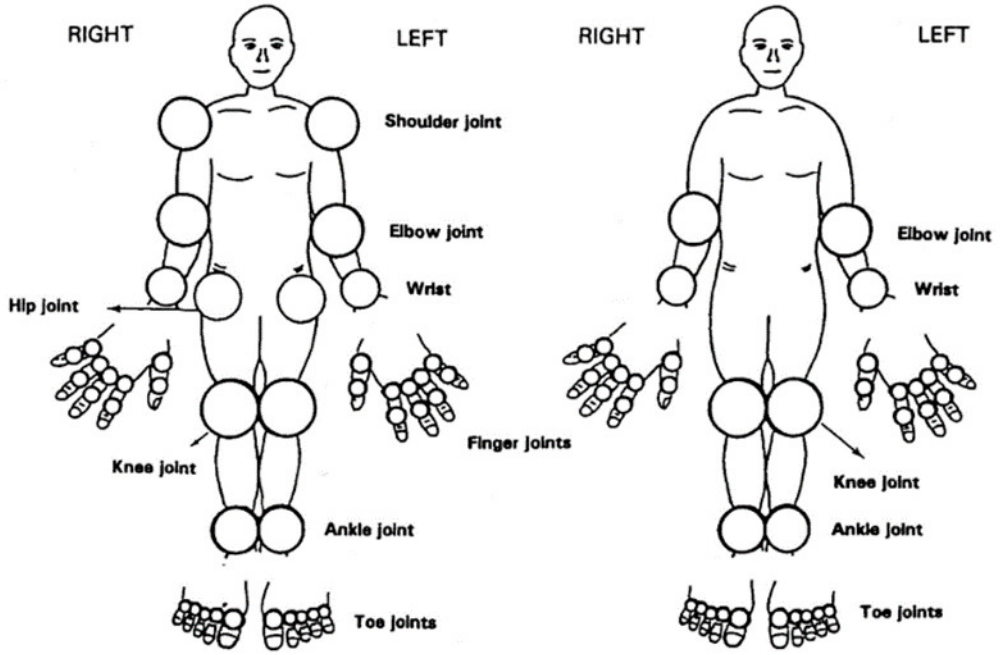
Samples that result in discordant results between local and central laboratories will be evaluated and discussed with the Investigator and the Sponsor's Medical Monitor on a case-by-case basis to determine whether the subject should continue on study or discontinue.

#### 9.5.1.2 Tender and Swollen Joint Counts

Tender and swollen (excludes hip) joint counts will be recorded at the Week -6 Visit (prior to the first dose of MTX); prior to pegloticase infusion at the Day 1 and Weeks 6, 14, 20, 24, 30, 36 and 44 Visits during the pegloticase + IMM Period; and at the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of Study/Early Termination Visit (Section 2.1).

Tender and swollen joint counts assessed by physical examination and documented using the rheumatoid arthritis 66-68 method shown in Figure 9.2 or other site source document. All information will be entered into the appropriate eCRF.

**Figure 9.2 Rheumatoid Arthritis 66-68 Tender and Swollen Joint Counts**




#### 9.5.1.3 Physician Global Assessment

The physician global assessment will be collected at the Screening and Week -6 (prior to the first dose of MTX) Visits; prior to pegloticase infusion at the Day 1 and Week 6, 14, 20, 24, 30,36 and 44 Visits during the Pegloticase + IMM Period; and at the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of Study/Early Termination Visit (Section 2.1). The physician will respond to the statement, "Considering the subject's overall health related to gout, rate their

gout overall" using a numeric rating scale ranging from 0 (excellent) to 10 (very poor) (see Appendix 17.3).

For a given subject, if possible, the same qualified Investigator should perform the assessment at each time point.

#### 9.5.1.4 Dual-energy Computed Tomography (DECT)

For sites with DECT capability, and subjects who provide consent, an optional DECT will be obtained at Day 1 and Weeks 14, 24 and at the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of Study/Early Termination Visit. The DECT may be completed within +/- 5 days of the scheduled timepoint.

Subjects who end pegloticase infusions prior to Week 52 should follow the scheduled timepoints but avoid a repeat DECT scan within 6 weeks of a prior scan (detailed guidance is provided with the imaging manual).

Images will be obtained for the hands and feet, and the Investigator will identify the primary area of major urate deposition. The imaging will be performed by a study-specific, qualified radiologist.

#### 9.5.1.5 X-ray of Hands and Feet

For sites with X-ray capability, and subjects who provide consent, an optional X-ray of the hands and feet will be obtained at Day 1, Week 24 and End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visit.

Subjects who end pegloticase infusions prior to Week 52 should follow the scheduled timepoints but avoid a repeat X-ray within 3 months of a prior X-ray (detailed guidance is provided with the imaging manual).

#### 9.5.1.6 Digital Photography

Digital photography of the hands and feet will be completed at Week -6, Day 1 and Weeks 14, 24, 36, and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination and the 3 and 6 month Post Treatment Follow-up Visits. Other anatomical sites with large tophi may be photographed in addition to the hands and feet at the Investigator's discretion.

The sponsor or designee will provide digital photography equipment to each site for photography of the hands and feet.

Details on the digital photography, including source documentation and eCRF requirements will be provided in the Study Reference Binder.

##### 9.5.1.6.1 Assessment of Individual Tophi Response

All measurable tophi will be measured bi-dimensionally (using the longest diameter and the longest perpendicular to that diameter) and the response of each individual tophus will be categorized according to the change from baseline in area of each tophus at each visit as follows:

- Complete Response (CR) – A 100% decrease in the area of the tophus

- Marked Response (MR) – At least a 75% decrease in the area of the tophus
- Stable Disease (SD) – Neither a 50% decrease nor a 25% increase in the area of the tophus can be demonstrated
- Progressive Disease (PD) – A 25% or more increase in the area of the tophus
- Unable to Evaluate (UE) –The tophus cannot be accurately measured for any reason at any given post-baseline time point (e.g., image missing or of poor quality, obvious infection of the tophus).

Each individual unmeasured tophus will be semi-quantitatively assessed based upon the impression of the central reader using the following guideline:

- Complete Response - the disappearance of the tophus.
- Improved - An approximate 50% or more reduction from baseline in the size of the tophus.
- Stable Disease – Neither improvement nor progression from baseline can be determined
- Progressive Disease - An approximate 50% or more increase from baseline in the area of the tophus.
- Unable to Evaluate - The tophus cannot be assessed for any reason at any given post-baseline time point (e.g., image missing or of poor quality, or obvious infection of the tophus).

The overall response for a subject will be based upon the best response among all tophi (including measurable and unmeasured) for that subject (e.g., if any one tophus shows complete response, the overall response is Complete Response). If any single tophus shows progression, or if a new tophus appears during the study, the overall response for that subject will be Progressive Disease, regardless of the response of any other tophi. New tophi arising outside of the regions photographed at baseline will be captured by the Investigator on the case report form, and will also result in an overall response assessment of Progressive Disease.

### 9.5.2 Quality of Life Assessment

The HAQ (Appendix 17.2) including the HAQ-DI, pain and health scales, will be administered at the Screening and Week -6 (prior to the first dose of MTX) Visits; prior to pegloticase infusion at the Day 1 and Weeks 6, 14, 20, 24, 30, 36 and 44 Visits during the Pegloticase + IMM Period; and at the End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and 3 and 6 month Post Treatment Follow-up Visits (Section 2.1).

The HAQ-DI is a self-report functional status instrument that can be filled out by a subject in less than 5 minutes and requires 1 minute to score. The index measures disability over the past week by asking a total of 20 questions covering 8 domains of function: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. There are at least 2 questions in each domain and the 8 domains represent a comprehensive set of functional activities. The HAQ-DI is calculated by scoring the answer to each question in the HAQ from 0 to 3, with 0 representing the ability to do without any difficulty, and 3 representing inability to do. Any activity that requires assistance from another individual or requires the use of an assistive device raises a 0 or 1 score to a

2. The highest score for each of the 8 domains is summed (range from 0 to 24) and divided by 8 to yield, on a scale with 25 possible values, a Functional Disability Index with a range from 0 to 3. The disability index is based on the number of domains answered and is computed only if the subject completes answers to at least 6 domains [Bruce and Fries, 2003].

The HAQ pain scale consists of a doubly anchored, horizontal visual analog scale (VAS), that is scored from 0 (no pain) to 100 (severe pain). Subjects are asked to rate the severity of the pain they have had because of illness in the past week by placing a vertical mark on the VAS.

The HAQ health scale consists of a doubly anchored, horizontal VAS, that is scored from 0 (very well) to 100 (very poor). Subjects are asked to rate how well they are doing, considering all the ways arthritis affects him or her, by placing a vertical mark on the VAS.

### 9.5.3 Pharmacokinetic and Anti-drug Antibody Measurements

Serum samples for PK analysis of pegloticase will be collected after the end of infusion on Day 1 (prior to discharge); prior to the pegloticase infusion and after the end of infusion (prior to discharge) at the Weeks 2, 6, 14, 24, 36; and at the non-infusion Week 21 Visit and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visits.

Serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 2, 6, 14, 22, 24, 36, and at the non-infusion End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of Study/Early Termination Visit and Month 3 Post Treatment Follow-up Visits.

Blood samples will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period for MTX Polyglutamate analysis.

Each sample collection date and time will be recorded in source documents and the eCRF.

Detailed instructions regarding blood sample timing and handling are provided in the Laboratory Manual.

#### 9.5.3.1 Additional Sample Collection for Future Use

Optional blood samples for PBMC, RNA isolation and serum will be collected from each consenting subject prior to the first dose of MTX at Week -6, prior to the infusion on Day 1 and Weeks, 6, 14, 24, 36 and the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End-of-Study/Early Termination. During visits at Weeks 2, 4, 8, 10 and 12, optional samples will only be collected if subjects are experiencing an acute gout flare on the day of visit.

Subjects may still participate in the study even if they decline to provide consent for the optional future use blood samples.

Samples will be retained for potential future analyses which may include biomarkers relevant to gout (e.g. inflammatory markers) or gout co-morbidities in response to pegloticase or other potential treatments for gout.

The samples will be retained no longer than 15 years after study completion or as required by applicable law. The samples will be stored in a secured storage space with adequate measures to protect confidentiality.

Detailed instructions regarding blood sample timing and handling are provided in the Laboratory Manual.

### 9.5.4 Safety Variables

Safety will be assessed via AE and concomitant medication use monitoring, physical examinations, vital signs, clinical safety laboratory evaluations (complete blood count, chemistry, urine albumin:creatinine ratio), pregnancy testing (if applicable), electrocardiograms (ECGs), and AEs of special interest (i.e., IRs, anaphylaxis, gout flares, and cardiovascular events).

#### 9.5.4.1 Adverse Events

##### 9.5.4.1.1 Definitions

###### 9.5.4.1.1.1 Adverse Event Definition

As defined by the ICH, an AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product, whether or not the event is considered related to the study drug. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Examples of an AE include:

- Conditions newly detected or diagnosed after the signing of the ICF, including conditions that may have been present but undetected prior to the start of the study
- Conditions known to have been present prior to the start of the study that worsen after the signing of the ICF
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se should not be reported as an AE)

Issues that will not be considered an AE include:

- Conditions present at the start of the study, should be recorded as medical history
- Medical or surgical procedures (e.g., endoscopy, appendectomy; however, a condition that leads to a procedure is an AE if it qualifies according to the definitions above)
- Situations where an untoward medical occurrence did not occur (e.g., social, diagnostic, elective, or convenience admission to a hospital)

- Fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not represent a clinically significant change from baseline
- Abnormal laboratory or test findings that are not assessed by the Investigator as a clinically significant change from baseline

AEs are divided into the categories "serious" and "non-serious." This determines the procedures that must be used to report/document the AE.

#### 9.5.4.1.1.2 Serious Adverse Event Definition

Based on ICH guidelines, an SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
  NOTE: The term 'life threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe, prolonged, or untreated.
- Requires hospitalization or prolongation of existing hospitalization
  NOTE: Hospitalization signifies that the subject has been admitted to the hospital as an inpatient for any length of time. Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of SAEs and not resulting in hospital admission does not qualify for this category, but may be appropriately included in category g (see below). Complications that occur during hospitalization are usually AEs. If a complication prolongs hospitalization or fulfills any other serious criterion, the event will be considered as serious. When in doubt as to whether 'hospitalization' occurred, consult the Sponsor's Medical Monitor.
  Hospitalization will not be considered an AE in and of itself. It will be considered an outcome of an AE. Therefore, if there is no associated AE, there is no SAE. For example, hospitalization for elective or pre-planned treatment of a pre-existing condition that did not worsen from baseline will not be considered an AE.
- Results in persistent or significant disability/incapacity
  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may temporarily interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether expedited

reporting as serious is appropriate in other situations; specifically, important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These should usually be considered serious. Examples of such events are invasive cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. If in doubt as to whether or not an event qualifies as an 'important medical event,' consult the Sponsor's Medical Monitor.

#### 9.5.4.1.1.3 Non-Serious Adverse Event Definition

AEs that do not result in any of the outcomes listed in Section 9.5.4.1.1.2 are considered non-serious.

#### 9.5.4.1.1.4 Unexpected Adverse Event Definition

An AE or suspected adverse reaction is considered unexpected if it is not listed in the Reference Safety Information section of the Investigator's Brochure (for pegloticase) or US Prescribing Information (for MTX) or is not listed with the specificity or severity that has been observed. Unexpected, as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Reference Safety Information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### 9.5.4.1.1.5 Adverse Events of Special Interest

AEs of special interest include IRs, anaphylaxis, gout flares, and cardiovascular events. AEs of special interest will be collected on a separate eCRF that captures data related to each AE of special interest. An external adjudication committee will adjudicate the AESIs of IR, anaphylaxis and cardiovascular events.

**Infusion Reaction**

An IR will be defined as any infusion-related AE or cluster of temporally-related AEs, not attributable to another cause, which occur during the pegloticase infusion and for up to 2 hours post infusion. Other AEs that occur outside of the 2-hour window following the infusion may also be categorized as an IR at the Principal Investigator's discretion. Signs and symptoms of the IR and treatments administered will be documented in the medical record and in the eCRF, and will be adjudicated.

Examples of AEs not considered possible IRs include, but are not limited to: laboratory abnormalities that are unlikely to have occurred during or within 1 hour following the infusion (e.g., anemia), gout flares, most infectious diseases, or the recurrence or worsening of a known chronic medical problem identified in the subject's medical history.

**Anaphylaxis**

Any incidence of anaphylaxis should be reported as an SAE. Anaphylaxis will be defined using the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria [Sampson et al, 2006], and will be adjudicated:

1. 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; urticaria, and angioedema (of lips, tongue, or uvula) and ≥1 of the following:

    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue, uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy, abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours): systolic blood pressure <90 mmHg or >30% decrease from that subject's baseline.

**Gout Flares**

It is common for potent urate-lowering therapies to lead to acute attacks of gout. Gout flares will be confirmed through questioning or direct observation detailed in Section 9.5.4.8.

**Cardiovascular Events**

Cardiovascular adverse events will be collected as part of the AE collection. External adjudication will be conducted for major adverse cardiovascular events (MACE) and congestive heart failure. Refer to the Adjudication Committee Charter for the detailed definition.

#### 9.5.4.1.2 Documentation of Adverse Events

AE monitoring will begin from the signature of the ICF until the 6 month Post Treatment Follow-up Visit.

SAE monitoring will begin from the signature of the ICF until the 6 month Post Treatment Follow-up Visit.

Subjects will be questioned about AEs at each study visit, using nonspecific questions, such as "How have you been feeling since the last study visit?" AEs must be recorded on the AE eCRF and documented in the source record after the signing of the ICF.

#### 9.5.4.1.3 Intensity of Adverse Events

All AEs, both serious and non-serious, will be assessed for severity using the Rheumatology Common Toxicity Criteria v2.0 [Woodworth et al, 2007]. The scale displays Grades 1 through 4 with unique clinical descriptions of severity for each AE (including abnormal laboratory values) based on this general guideline.

- Grade 1 (mild) – asymptomatic or transient, short duration (<1 week), no change in lifestyle, no medication or over-the-counter
- Grade 2 (moderate) – symptomatic, duration 1 to 2 weeks, alter lifestyle occasionally, medications give relief (may be prescription), study drug continued
- Grade 3 (severe) – prolonged symptoms, reversible, major functional impairment, prescription medications/partial relief, hospitalized <24 hours, temporary study drug discontinuation or/and dose reduced
- Grade 4 (includes life-threatening) – at risk of death, substantial disability, especially if permanent, hospitalized >24 hours, permanent study drug discontinuation

#### 9.5.4.1.4 Relationship to Study Drug

The relationship of each AE to MTX/placebo for MTX and/or pegloticase will be determined by the Investigator and the Sponsor based on the following definitions:

- Not related: There is no plausible temporal relationship or there is another explanation that unequivocally provides a more plausible explanation for the event.
- Related: There is evidence in favor of a causal relationship (i.e., there is a plausible time course) and ≥1 of the following criteria apply:
    - There is a reasonable pharmacological relationship (or known class effect).
    - There is no other more plausible explanation.
    - There is a positive de-challenge (without active treatment of the event).
    - There is a positive re-challenge.

- There is a distinguishable dose effect.

The assessment of causality will be based on the information available and may change based upon receipt of additional information.

#### 9.5.4.1.5 Reporting and Documenting SAEs and Product Complaints

##### 9.5.4.1.5.1 Serious Adverse Events

Any death, life-threatening event, or other SAE experienced by a subject during the course of the study, whether or not judged drug-related, must be reported within 24 hours of knowledge of the event by entering the information into the eCRF. If unable to access the eCRF, the event must be reported by submitting the completed SAE form via email or fax to the contact numbers provided below.

Fax (800) 860-7836
E-mail clinicalsafety@horizonpharma.com

The event must be documented in source documentation and the eCRF. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to MTX/placebo for MTX and/or pegloticase:

1. Report the SAE to the Sponsor by entering the information into the eCRF within 24 hours after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form by email to clinicalsafety@horizonpharma.com or fax within 24 hours after becoming aware that a subject has experienced an SAE.
2. Perform appropriate diagnostic tests and therapeutic measures, and submit all follow-up substantiating data, such as diagnostic test reports, hospital discharge summaries, and autopsy report to the Sponsor's representative.
3. Respond in a timely manner to any queries from Sponsor regarding the SAE.
4. Conduct appropriate consultation and follow-up evaluation until the SAE is resolved, stabilized, or otherwise explained by the Investigator.
5. Review each SAE report and evaluate the relationship of the SAE to MTX/placebo for MTX and/or pegloticase.
6. The Investigator must report all AEs or SAEs that meet the criteria for Unanticipated Problems Involving Risks to Human Subjects or Others to the IRB.

After receipt of the initial report, the information will be reviewed and the Investigator may be contacted with requests for additional information or for data clarification.

Follow-up will be obtained via the eCRF, fax, or e-mail, as necessary, until the event resolves or attains a stable outcome. Horizon or designee is responsible for the preparation of MedWatch 3500 A/Council for International Organizations of Medical Sciences I forms and

analysis of similar events for individual occurrences (to be submitted as Investigational New Drug [IND] safety letters to the FDA and Investigators according to 21 CFR 312.32 by Horizon).

#### 9.5.4.1.5.2 Product Complaints

A product complaint process will be described in the Study Reference Manual. Any product complaint must be reported to the Sponsor using this process.

#### 9.5.4.1.6 Follow-up of Adverse Events

Once the study-defined, non-serious AE (6 month Post Treatment Follow-up Visit) and SAE reporting periods have passed (i.e., 6 month Post Treatment Follow-up Visit), reporting is required only if an Investigator becomes aware of an SAE that he or she considers related to MTX/placebo for MTX and/or pegloticase.

After the initial recording of an AE, the Investigator should proactively follow the subject. Any non-serious AEs that are still ongoing at the end of the study should be reviewed to determine if further follow up is required. The Investigator will document on the AE eCRF all ongoing non-serious AEs that will not be followed further after the subject exits the study. If in doubt, the Investigator should consult the Sponsor's Medical Monitor.

All SAEs should be followed until resolution, until the condition stabilizes, or until the subject is lost to follow-up. Once the SAE is resolved, the corresponding AE eCRF page should be updated.

#### 9.5.4.1.7 Medication Error and Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to, or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of medication errors and overdose (with or without associated AEs) will be documented on the eCRF in order to capture this important safety information consistently in the database. AEs associated with an overdose and SAEs of overdose are to be reported according to the procedures outlined in Section 9.5.4.1.2 and Section 9.5.4.1.5, respectively.

In the event of drug overdose, the subject is to be treated as appropriate.

#### 9.5.4.1.8 Review of Adverse Events and Emerging New Safety Information

The Sponsor will notify all Investigators involved in the clinical investigation of important safety information regarding the study treatment, as required by the applicable regulations. Investigators will notify their IRB of all such notifications, as required.

#### 9.5.4.1.9 Reporting of IND Safety Reports

The Sponsor will notify the United States FDA and all Investigators on any new serious risks associated with the drug.

#### 9.5.4.1.10 Development Safety Update Reports

The Sponsor will prepare and submit annual safety reports to competent authorities.

### 9.5.4.2 Pregnancy Reporting

Women of childbearing potential (including those with an onset of menopause <2 years prior to the screening, non-therapy-induced amenorrhea for <12 months prior to the screening, or not surgically sterile [absence of ovaries and/or uterus]) will have a serum pregnancy test at the Screening Visit. Urine pregnancy tests will also be performed at all other time points, as indicated in Section 2.1. Pregnancy will not be considered an AE in this study, however, any pregnancy complications, including an elective termination for medical reasons, should be reported as an AE.

Information must be obtained and reported if a female subject suspects that she has become pregnant during the study (including the MTX Tolerability Assessment and Run-in Periods) up to 30 days after the last dose of study treatment (either pegloticase or MTX or placebo for MTX), or if a female partner of male subject suspects that she has become pregnant during the study (including the MTX Tolerability Assessment and Run-in Periods) up to 3 months (approximately 90 days) after their male subject partner discontinues MTX or placebo for MTX. The Investigator will instruct the female subject to stop taking all study drugs. A serum pregnancy test should be performed if any female subject or female partner of a male subject suspects that she has become pregnant during the time frame as defined above. If pregnancy is confirmed, female subject will be withdrawn from the study. Pregnancy will be followed up until the outcome of pregnancy.

Complete pregnancy information, including the outcome of the pregnancy, should be collected in the source documents on the female subject or partner of a male subject. In the absence of complications, follow-up after delivery will be no longer than 8 weeks. Any stillbirths or premature terminations of pregnancies, whether elective, therapeutic, or spontaneous, should be reported on the pregnancy outcome form. Any pregnancy complications, including an elective termination for medical reasons, should be reported as an AE.

A spontaneous abortion should always be considered an SAE, as should any congenital defects in the newborn. Any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the Investigator should be reported to the Sponsor.

Women who are breastfeeding are not eligible to participate in the study.

#### 9.5.4.3 Medical History

Medical history, including gout history (e.g., time of first diagnosis and history of tophi, collected on a gout-specific eCRF) and symptom severity, will be conducted at the Screening Visit.

#### 9.5.4.4 Vital Signs, Height, and Weight

Routine vital signs, including blood pressure, respiratory rate, temperature, and heart rate will be measured at Screening, Week -6, Week -4, Day 1 and Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and the End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and 3 and 6 month Post Treatment Follow-up Visits. Heart rate and blood pressure measurements should be taken after the subject has been in a sitting position and in a rested and calm state with proper positioning including back support, feet flat on the floor, for at least 5 minutes. Subject's arm should be supported at heart level; and cuff placed on the bare arm. A large cuff should be used as needed to fit the upper arm and a consistent arm is to be used at each study visit. The Korotkoff phase V will be used to determine diastolic blood pressure. During the Pegloticase + IMM Period study visits, vitals should be taken before the pegloticase infusion and any time after the end of the infusion, but prior to subject's discharge/release from the site.

At sites who participate and from subjects who consent, optional intensive blood pressure measurements will be taken prior to the infusion on Day 1 and at Weeks 6, 12, 18, 24, 30, 36, 42, 48 and at the non-infusion End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visit. At these intensive blood pressure collections, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained. All 3 values will be recorded in the eCRF.

When possible, the same staff member should take all BP measurements for a given subject.

Weight should be measured in kilograms or pounds without shoes and recorded at the Screening Visit and prior to dosing MTX Week -6 Visit; prior to pegloticase infusion on Day 1 and at the Weeks 8, 16, 24, 36 and at the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and Months 3 and 6 Post Treatment Follow-up Visits.

Height will be collected at the Screening Visit only.

Vital sign monitoring during IR is described in Section 9.4.6.3.2.4.

#### 9.5.4.5 Physical Examinations

A complete physical examination will be performed at the Screening Visit, including assessment of HEENT, heart, lungs, abdomen, skin, extremities, neurological status and musculoskeletal including an assessment for the presence of tophi.

A targeted physical examination per investigator judgement will be conducted at Week -6, Day 1, and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20, 24, 36 and the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and 3 and 6 month Post Treatment Follow-up Visits; at a minimum this should include heart, lungs, and abdominal exam.

Clinically significant findings from the targeted physical examinations will be recorded as AEs.

#### 9.5.4.6 Electrocardiogram

A 12-lead ECG will be performed at Screening and at the discretion of the Investigator thereafter.

#### 9.5.4.7 Clinical Laboratory Safety Tests

Blood (for hematology and clinical chemistry) will be collected at the Screening, Week -6 (prior to the first dose of MTX), and Week -4 and -2 Visits during the Run-in Period; prior to pegloticase infusion on Day 1 and at the Weeks 2, 6, 14, 22, 24, 36 and the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and 3 and 6 month Post Treatment Follow-up Visits.

Urine (for albumin:creatinine ratio and allantoin acid) samples will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 14, 24, 36 and the non-infusion End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visits.

Urine (for human chorionic gonadotropin) samples will be collected at all visits except the Screening Visit and Weeks 21, 23 and 3 and 6 month Post Treatment Follow-up Visits for all female subjects of childbearing potential.

Safety laboratory assessments will include:

- Hematology: complete blood count with differential (hemoglobin concentration, hematocrit, erythrocyte count, platelet count, leukocyte count, and differential leukocyte count)

- Chemistry: albumin, transaminases (aspartate aminotransferase, alanine aminotransferase), alkaline phosphatase, total bilirubin, creatinine (including calculation for eGFR calculated by the MDRD study equation : $175 \times (S_{cr[mg/dL]})^{-1.154} \times (age)^{-0.203} \times$ (0.742 if female) x (1.212 if African American) or $175 \times (S_{cr[\mu mol/L]}/88.4)^{-1.154} \times (age)^{-0.203} \times$ (0.742 if female) x (1.212 if African American), glucose, sodium, potassium, calcium, chloride, total protein, blood urea nitrogen, and human chorionic gonadotropin (at the Screening Visit for all female subjects of childbearing potential)

- Urine: albumin:creatinine ratio, allantoin acid and human chorionic gonadotropin for all female subjects of childbearing potential

Safety laboratory samples will be analyzed by the central laboratory. Samples will be collected for analysis at the local laboratory, if needed.

#### 9.5.4.8 Assessment of Gout Flare

There is no validated instrument to assess gout flares. Gout flares will be assessed at the time points specified in Section 2.1. Investigators will assess gout flares based on subject self-reporting, with investigator confirmation of flare based on subject questioning and/or direct observation. All gout flares will be recorded as adverse events with the required AE reporting information. Investigators will also ask the subject a series of questions related to each gout flare, to document subject report of swollen joints, joints that are warm to touch, and level of joint pain [Gaffo et al, 2012].

### 9.5.5 Data Monitoring Committee (DMC)

An external Data Monitoring Committee (DMC) will be convened to review data for safety and efficacy, with the possibility of DMC recommendation on study design modification per pre-defined charter.

### 9.5.6 Adjudication Committee

One clinical adjudication committee will be established for this study to adjudicate the adverse events of special interest (AESIs) defined in the protocol (See 9.5.4.1.1.5) which include infusion reactions, anaphylaxis and cardiovascular events. The AESI of gout flare will not be adjudicated. The committee will be comprised of physicians with experience in immunology, allergic reactions, rheumatology, and cardiovascular diseases. Periodically the adjudication committee will review all AESIs. Details outlining the responsibilities of the adjudication committee will be included in the adjudication committee charter.

### 9.5.7 Appropriateness of Measurements

The study population is well-defined and is consistent with the expected target population for whom pegloticase is indicated (adult subjects with uncontrolled gout and with the ability to tolerate MTX or placebo for MTX).

### 9.5.8 Study Procedures

Subjects who provide informed consent and who meet all the entry criteria for participation in this study will be enrolled.

#### 9.5.8.1 Screening/MTX Tolerability Assessment/Run-in Period

During the Screening/MTX Tolerability Assessment Period, study candidates will be evaluated for study entry according to the stated inclusion and exclusion criteria (Section 9.3). The following procedures will be performed during screening to establish each candidate's eligibility for enrollment into the study.

#### 9.5.8.1.1 Screening Visit (Within 2 Weeks Prior to the First Dose of MTX at Week -6)

- Obtain signed, written informed consent. Refusal to provide this permission excludes an individual from eligibility for study participation. Record date informed consent was given and who conducted the process on the appropriate source documentation.
- Determine study eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Obtain demographic information
- Investigator review of clinical status and subject treatment goals.
- Collect complete gout history (on gout-specific CRF), other relevant medical/surgical history, and medication history, including gout medications starting at the time of diagnosis and up to screening (on gout medications-specific CRF), substance use history, and all other medications currently being taken at screening (see Section 9.4.10 for restrictions regarding medications).
- Chest X-ray for subjects that do not have a chest X-ray within 2 years prior to Screening if deemed necessary by the Investigator.
- Perform a complete physical examination, including assessment of HEENT, heart, lungs, abdomen, skin, extremities, neurological status and musculoskeletal including an assessment for the presence of tophi.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate), (see Section 9.5.4.4).
- Record height and weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a serum sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples to evaluate sUA (only 1 sample for central laboratory) and G6PD.
- Administer HAQ and record physician global assessments.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.1.2 Week -6 (MTX Tolerability Assessment Period)

- Confirm study eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) (see Section 9.5.4.4).
- Record weight.
- Document gout flares and intensity.
- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.
- Digital photography of hands and feet.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain a blood sample for measurement of sUA (only 1 sample for central laboratory).
- Obtain optional whole blood and serum samples from subjects who consent for future analysis.
- Provide dosing calendar for subjects to record the date and time they take MTX/placebo for MTX. (Additional calendar pages may be provided at future visits as needed).
- Dispense MTX.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Inquire about AEs and concomitant medication use.
- Subjects that take MTX during Week -6 or Week -5, and who are females of childbearing potential, will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of MTX to verify at least one ovulatory cycle has occurred since the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. Subjects who are non-vasectomized males, an inquiry will be conducted approximately 3 months after MTX discontinuation regarding partner pregnancy.

#### 9.5.8.1.3 Week -4 (Run-in Period)

- Confirm study eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) (see Section 9.5.4.4).
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain a blood sample for measurement of sUA (only 1 sample for central laboratory).
- Assess MTX compliance (from MTX Tolerability Assessment Period)
- Dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid and gout flare prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Inquire about AEs and concomitant medication use.
- Randomization in RTMS to MTX or placebo for MTX.
- Subjects that take MTX/placebo for MTX during Week -4 or Week -3, and who are females of childbearing potential, will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of MTX/placebo for MTX to verify at least one ovulatory cycle has occurred since the last dose of MTX/placebo for MTX. If the subject has not ovulated, a urine pregnancy test will be performed. Subjects who are non-vasectomized males, an inquiry will be conducted approximately 3 months after MTX/placebo for MTX discontinuation regarding partner pregnancy.

#### 9.5.8.1.4 Week -2 (Run-in Period)

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain a blood sample for measurement of sUA (only 1 sample for central laboratory).

- Obtain blood samples for hematology and clinical chemistry analysis.
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid and gout flare prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Inquire about AEs and concomitant medication use.
- Subjects that take MTX/placebo for MTX during Week -2 or Week -1, and who are females of childbearing potential, will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of MTX/placebo for MTX to verify at least one ovulatory cycle has occurred since the last dose of MTX/placebo for MTX. If the subject has not ovulated, a urine pregnancy test will be performed. Subjects who are non-vasectomized males, an inquiry will be conducted approximately 3 months after MTX/placebo for MTX discontinuation regarding partner pregnancy.

#### 9.5.8.2 Pegloticase + IMM Period

##### 9.5.8.2.1 Day 1

On Day 1, subjects will return to the clinic for the following assessments and the first dose of pegloticase.

- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). During the pre-infusion blood pressure collection, at sites who participate and from subjects who consent, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.
- Record weight.
- Digital photography of hands and feet.
- For sites with X-ray capability, and subjects who provide consent, an optional X-ray of the hands and feet will be obtained.

- Document gout flares and intensity.
- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.
- For sites with DECT capability, and subjects who provide consent, an optional DECT will be obtained. DECT may be completed within +/- 5 days of the scheduled visit.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a urine sample for albumin:creatinine ratio and allantoin acid.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain 1 blood sample for measurement of sUA prior to the pegloticase infusion and after the end of the pegloticase infusion.
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Obtain blood samples for MTX Polyglutamate analysis prior to the infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Obtain optional whole blood and serum samples from subjects who consent for future analysis.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and solumedrol) (see Section 9.4.1.3).
- Administer the first dose of pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Obtain blood samples for pegloticase PK analysis any time after the end of the infusion, prior to discharge from the site.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.2 Week 2

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX within the previous 1 to 3 days.

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (see Section 9.5.4.4).

- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Obtain blood samples for hematology and clinical chemistry analysis.

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.

- Obtain blood samples for pegloticase PK analysis prior to the pegloticase infusion and any time after the end of the infusion, prior to discharge from the site.

- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.

- Obtain optional whole blood and serum samples from subjects who consent for future analysis. Samples will only be collected at this visit for subjects having an acute gout flare during this visit.

- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.

- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.

- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.3 Week 4

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.

- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).

- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.

- Obtain optional whole blood and serum samples from subjects who consent for future analysis. Samples will only be collected at this visit for subjects having an acute gout flare during this visit.

- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.

- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.4 Week 6

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). During the pre-infusion blood pressure collection, at sites who participate and from subjects who consent, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.

- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain optional whole blood and serum samples from subjects who consent for future analysis.
- Obtain blood samples for pegloticase PK analysis prior to the pegloticase infusion and any time after the end of the infusion, prior to discharge from the site.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.5 Week 8

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).

- Record weight.

- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.

- Obtain optional whole blood and serum samples from subjects who consent for future analysis. Samples will only be collected at this visit for subjects having an acute gout flare during this visit.

- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.

- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.6 Week 10

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).

- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.

- Obtain optional whole blood and serum samples from subjects who consent for future analysis. Samples will only be collected at this visit for subjects having a gout flare during this visit.

- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.

- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.

- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.7 Week 12

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.

- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). During the pre-infusion blood pressure collection, at sites who participate and from subjects who consent, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain optional whole blood and serum samples from subjects who consent for future analysis. Samples will only be collected at this visit for subjects having an acute gout flare during this visit.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.8 Week 14

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center

other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

  - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.
- Digital photography of hands and feet.
- For sites with DECT capability, and subjects who provide consent, an optional DECT will be obtained. DECT may be completed within +/- 5 days of the scheduled visit.
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a urine sample for albumin:creatinine ratio and allantoin acid.
- Obtain blood samples for pegloticase PK analysis prior to the pegloticase infusion and any time after the end of the infusion, prior to discharge from the site.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Obtain blood samples for MTX Polyglutamate analysis prior to the infusion.

- Obtain optional whole blood and serum samples from subjects who consent for future analysis.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.9 Week 16

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Record weight.
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.10 Week 18

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). During the pre-infusion blood pressure collection, at sites who participate and from subjects who consent, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.11 Week 20

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.12 Week 21

- Obtain a blood sample (1 sample) for measurement of sUA.
- Obtain blood samples for pegloticase PK analysis.
- Inquire about AEs and concomitant medication use.
- Document gout flares and intensity.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

#### 9.5.8.2.13 Week 22

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.

- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.14 Week 23

- Obtain a blood sample (1 sample) for measurement of sUA
- Inquire about AEs and concomitant medication use.
- Document gout flares and intensity.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

#### 9.5.8.2.15 Week 24

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.
- Investigator review of clinical status and subject treatment goals.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). During the pre-infusion blood pressure collection, at sites who participate and from subjects who consent, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.
- Record weight.
- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.
- Digital photography of hands and feet.
- For sites with DECT capability, and subjects who provide consent, an optional DECT will be obtained. DECT may be completed within +/- 5 days of the scheduled visit.
- For sites with X-ray capability, and subjects who provide consent, an optional X-ray of the hands and feet will be obtained.

- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a urine sample for albumin:creatinine ratio and allantoin acid.
- Obtain blood samples for pegloticase PK analysis prior to the pegloticase infusion and any time after the end of the infusion, prior to discharge from the site.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Obtain blood samples for MTX Polyglutamate analysis prior to the infusion.
- Obtain optional whole blood and serum samples from subjects who consent for future analysis.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.16 Week 26

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

- Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.17 Week 28

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.18 Week 30

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). During the pre-infusion blood pressure collection, at sites who participate and from subjects who consent, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.

- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.

- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.

- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.19 Week 32

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.20 Week 34

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.

- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.21 Week 36

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.

- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). During the pre-infusion blood pressure collection, at sites who participate and from subjects who consent, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.
- Record weight.
- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.
- Digital photography of hands and feet.
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a urine sample for albumin:creatinine ratio and allantoin acid.
- Obtain blood samples for pegloticase PK analysis prior to the pegloticase infusion and any time after the end of the infusion, prior to discharge from the site.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Obtain blood samples for MTX Polyglutamate analysis prior to the infusion.
- Obtain optional whole blood and serum samples from subjects who consent for future analysis.

- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.

- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.

- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.22 Week 38

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).

- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.

- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.

- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.23 Week 40

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).

- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.

- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.

- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.24 Week 42

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). During the pre-infusion blood pressure collection, at sites who participate and from subjects who consent, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.25 Week 44

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.26 Week 46

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.27 Week 48

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center

other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).

- Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.

- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). During the pre-infusion blood pressure collection, at sites who participate and from subjects who consent, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.

- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.

- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.

- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.

- Inquire about AEs and concomitant medication use.

#### 9.5.8.2.28 Week 50

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to this visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion. If a local laboratory sample is drawn at a center other than the research site (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit (see Section 9.5.1.1).
    - Stopping rule: Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- Administer MTX/placebo for MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX/placebo for MTX within the previous 1 to 3 days.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Assess MTX/placebo for MTX compliance and re-dispense MTX/placebo for MTX.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10-mL flush) times of dosing.
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site.
- Inquire about AEs and concomitant medication use.

**Note:** MTX will be taken one week following the Week 50 Visit and Folic Acid will be taken until just prior to the Week 52 Visit.

#### 9.5.8.3 End of Pegloticase Infusions Visit

Subjects who end pegloticase infusions prior to Week 52 will complete the End of Pegloticase Infusions Visit procedures following their final infusion. Subjects should continue to participate in all visits through the end of the study. Subjects must complete selected study visits at the study site during key efficacy and safety collections at Weeks 12, 13, 14, 20, 21, 22, 23, 24, 32, 34, 36, 48, 50 and 52, so that sUA labs and other key assessments can be completed. During visits between these key efficacy and safety collection visits, in subjects who have stopped infusions, subjects may complete study visits in person or via a telephone visit option to collect AEs, conmeds and gout flare information (See 9.3.3.1.1).

The following procedures will be completed at the End of Pegloticase Visit:

- Investigator review of clinical status and subject treatment goals.
- Document gout flares and intensity.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). At sites that participate and from subjects who consent, during the BP collection, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.
- Record weight.
- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.
- Assess MTX/placebo for MTX compliance.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis compliance.
- Digital photography of hands and feet.
- For sites with DECT capability, and subjects who provide consent, an optional DECT will be obtained. DECT may be completed within +/- 5 days of the scheduled visit. Subjects who end pegloticase infusions prior to Week 52 should follow the scheduled timepoints but avoid a repeat DECT scan within 6 weeks of a prior scan.

- For sites with X-ray capability, and subjects who provide consent, an optional X-ray of the hands and feet will be obtained. Subjects who end pegloticase infusions prior to Week 52 should follow the scheduled timepoints but avoid a repeat X-ray within 3 months of a prior X-ray.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a urine sample for albumin:creatinine ratio and allantoin acid.
- Obtain blood samples for pegloticase PK analysis.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies.
- Obtain optional whole blood and serum samples from subjects who consent for future analysis.
- Obtain a blood sample (1 sample) for measurement of sUA.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.4 Week 52/End of Study/Early Termination Visit

- Investigator review of clinical status and subject treatment goals.
- Document gout flares and intensity.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4). At sites that participate and from subjects who consent, during the BP collection, optional intensive BP collections will be obtained. For this optional collection, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a second set of 3 sitting blood pressure measurements will be obtained.
- Record weight.
- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.

- Digital photography of hands and feet.
- For sites with DECT capability, and subjects who provide consent, an optional DECT will be obtained. DECT may be completed within +/- 5 days of the scheduled visit.
- For sites with X-ray capability, and subjects who provide consent, an optional X-ray of the hands and feet will be obtained.
- Assess MTX/placebo for MTX compliance.
- Ask Yes/No question regarding folic acid compliance.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a urine sample for albumin:creatinine ratio and allantoin acid.
- Obtain blood samples for pegloticase PK analysis.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies.
- Obtain optional whole blood and serum samples from subjects who consent for future analysis.
- Obtain a blood sample (1 sample) for measurement of sUA.
- Inquire about AEs and concomitant medication use.

#### 9.5.8.5 Safety Follow-up Phone/Email Visits

Thirty (30) days after the last pegloticase infusion, subjects will be contacted by telephone or email to inquire about SAEs. Subjects who are females of childbearing potential will be asked to confirm that ovulation has occurred. If the subject has not ovulated, the subject will be requested to return to the site for a urine pregnancy test.

#### 9.5.8.6 MTX Partner Pregnancy Follow-up

Subjects who are non-vasectomized males will be asked 3 months after MTX or placebo for MTX discontinuation regarding partner pregnancy. This will occur at a scheduled visit or by a phone/email visit.

#### 9.5.8.7 Post Treatment Follow-up

The intent is to obtain at least 6 months of follow-up on each subject after cessation of pegloticase infusions. If these 6 months occur prior to end of study at Week 52, such as in the case of a subject who ends pegloticase infusions on or before Week 24, there will be no follow-

up visits after the Week 52/End of Study Visit. For subjects who end pegloticase infusions between Weeks 26 and 36, there will be at least 3 months of follow-up while the subject remains on-study prior to Week 52, and then one follow-up visit after the Week 52/End of Study Visit. For subjects who end pegloticase infusions between Weeks 38 and 52, there will be two follow-up visits at intervals of 3 months apart after the Week 52/End of Study Visit. The following procedures will be completed at the 3 and 6 month Post Treatment Follow-up Visits:

- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to discharge. (See Section 9.5.4.4).
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record weight.
- Collect swollen/tender joint counts; administer HAQ; and record physician global assessments.
- Digital photography of hands and feet.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a blood sample (1 sample) for measurement of sUA.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies (3 Month Post Treatment Follow-up Visit only).
- Inquire about AEs and concomitant medication use.

## 9.6 Statistical Methods and Determination of Sample Size

### 9.6.1 Endpoints

#### 9.6.1.1 Primary Endpoint

The primary efficacy endpoint is the proportion of Month 6 (Weeks 20, 21, 22, 23 and 24) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.

#### 9.6.1.2 Secondary Endpoints

The secondary efficacy endpoints (analyzed sequentially) are:

1. The proportion of Month 9 (Weeks 32, 34, and 36) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 9.

2. The proportion of Month 12 (Weeks 48, 50, and 52) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 12.

3. The proportion of subjects with complete resolution of ≥ 1 tophi (using digital photography) at Week 52 in subjects with tophi at baseline.

#### 9.6.1.3 Exploratory Endpoints

The exploratory efficacy endpoints are:

- The mean change from baseline to Weeks 24, 36, and 52 in urate deposition volume and bone erosions due to gout based on DECT of the hands and feet.
- The mean change from baseline to Weeks 14, 24, and 52 in bone erosions due to gout based on X-rays of the hands and feet.
- The proportion of subjects with complete resolution of ≥ 1 tophi (using digital photography) at Weeks 24 and 36 in subjects with tophi at baseline.
- The mean change from baseline in tophus size (long axis measured using digital photography) to Weeks 14, 24, 36 and 52 in subjects with tophus present at baseline.
- The proportion of Month 3 (Weeks 10, 12, and 14) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 3.
- The proportion of overall responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 3 (Weeks 10, 12, and 14) and Month 6 (Weeks 20, 21, 22, 23 and 24) combined.
- The proportion of 5 mg/dL responders during each time interval (Month 3, Month 6, Month 9 and Month 12), defined as subjects achieving and maintaining sUA <5 mg/dL for at least 80% of the time during each time interval.
- The mean change from baseline in sUA at Weeks 14, 24, 36 and 52.
- The time to first sUA > 6 mg/dL.
- The time to two consecutive sUA > 6 mg/dL (stopping rule).
- The percentage of non-hyperuricemic (sUA < 6 mg/dL) time during Months 3, 6, 9 and 12.
- The mean change from baseline in HAQ Pain score at Weeks 14, 24, 36 and 52.
- The mean change from baseline in HAQ Health score at Weeks 14, 24, 36 and 52.
- The mean change from baseline in HAQ-DI score at Weeks 14, 24, 36 and 52.
- The mean change from baseline in tender joint count (68-point scale) at Weeks 14, 24, 36 and 52.
- The mean change from baseline in swollen joint count (66-point scale) at Weeks 14, 24, 36 and 52.
- The mean change from baseline in number of tender or swollen joints at Weeks 14, 24, 36 and 52.

- The mean change from baseline in physician global assessment of gout at Weeks 14, 24, 36 and 52.
- The proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36 and 52.
- The proportion of subjects whose treatment goals are met at Weeks 24 and 52.
- The mean change from baseline in SBP and DBP to each visit.

#### 9.6.1.4 Pharmacokinetic and Anti-drug Antibody Endpoints

The PK and anti-drug antibody endpoints are:

- PK of pegloticase.
- The incidence of anti-PEG and anti-Uricase IgG antibodies.

#### 9.6.1.5 Safety and Tolerability Endpoints

Safety and tolerability objectives are:

- AE/SAE profile overall and potentially attributed to the combination of pegloticase and MTX
    - Incidence of AESI: IRs, anaphylaxis, gout flares, cardiovascular events
- Laboratory tests
- Vital signs and physical examination

### 9.6.2 Populations for Analysis

The following analysis populations will be defined for this study:

- Intent-to-treat population (ITT): all randomized subjects
- Modified intention-to-treat (mITT) population: all randomized subjects who receive at least 1 dose of pegloticase
- Per-protocol population (PP): all randomized subjects who receive at least 1 dose of pegloticase, are taking the 15 mg dose of MTX or placebo for MTX at the time of first pegloticase dose, and have no major protocol deviations that would challenge the validity of the data
- Pharmacokinetic (PK) population: all randomized subjects who receive at least one dose of pegloticase and have a post-pegloticase sample evaluable for PK analysis
- Safety population: all randomized subjects who take at least one dose of blinded MTX or placebo for MTX
- MTX population: all subjects who take at least one dose of MTX

The ITT and mITT populations will be used for analysis of efficacy data; subjects will be analyzed according to the treatment to which they were randomized. The PP population will be

used for analysis of select efficacy endpoints; subjects will be analyzed according to the treatment received. The safety population will be used for analysis of safety data; subjects will be analyzed according to the treatment received. The MTX population will be used for analysis of safety data during the Run-In period prior to randomization.

### 9.6.3 Demographic Variables

Demographic data, including age, race, and gender, medical history, and other disease characteristics, will be summarized using descriptive statistics. Listings will include all screened subjects.

### 9.6.4 Subject Disposition

The number of subjects in each population and the number and percentage of subjects who completed the study and who discontinued the study prematurely along with the reasons for discontinuation will be summarized for each study period.

### 9.6.5 Efficacy Endpoint Analysis

Efficacy analyses will be performed using the ITT and mITT populations, with select endpoints analyzed using the PP population. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages. Unless otherwise specified, baseline is defined as the last non-missing observation prior to the first dose of MTX.

#### 9.6.5.1 Primary and Secondary Endpoint Analysis

The primary analysis will be conducted in the ITT population. The primary efficacy endpoint is the proportion of responders during Month 6. A responder is defined as a subject for whom the proportion of time that the sUA-time curve is <6 mg/dL during the analysis interval is at least 80%. The proportion of time that the sUA level is below 6 mg/dL is defined as the ratio of the time during which the sUA level remains below 6 mg/dL (using linear interpolation, if necessary) to the entire time interval during Month 6. A subject will be declared a non-responder if the subject had 2 sUA levels >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit prior to or during Month 6. Additionally, a subject who withdraws from study treatment for any reason other than the stopping rule after randomization and prior to or during Month 6 (for the primary endpoint) or Months 9 or 12 (for the secondary endpoints) will be considered a non-responder at the time of withdrawal (and for all subsequent time points) if sUA values are not collected at the planned time points. Sensitivity analyses of the primary and secondary endpoints will include data (if available) for subjects who discontinue treatment due to stopping rule and remain on study.

The analysis of the primary endpoint and the secondary responder endpoints will assess risk difference (difference in response proportions) in a stratified analysis. The analysis will use Cochran-Mantel-Haenszel (CMH) weighting to estimate the common risk difference within strata and to estimate the standard error of the common risk difference. Stratification for the analysis will use the same factor as was used to stratify randomization, presence of tophi (yes, no). The difference in response rates, comparing pegloticase with MTX vs. pegloticase with

placebo for MTX, will be estimated along with the corresponding 95% confidence interval (CI) and p-value.

Subjects with resolution of ≥ 1 tophi are subjects with an overall tophus response of complete response (i.e. complete response in at least one tophi and no evidence of progressive disease, see Section 9.5.1.6.1). The difference in the proportion of subjects with resolution of ≥ 1 tophi at Week 52 between pegloticase with MTX and pegloticase with placebo for MTX will be tested with a chi-square test, and the difference in rates will be estimated along with the corresponding 95% confidence interval (CI) and p-value.

To control the overall Type 1 error rate of the study, taking into consideration the one primary and 3 secondary endpoints, the endpoints will be tested sequentially. For each endpoint, pegloticase with MTX will be tested against pegloticase with placebo for MTX at the 0.05 level only if pegloticase with MTX was statistically significant for the endpoint preceding it in the prespecified order and 3 secondary endpoints, the endpoints will be tested sequentially. For each endpoint, pegloticase with MTX will be tested against pegloticase with placebo for MTX at either the 0.05 level only if pegloticase with MTX was statistically significant for the endpoint preceding it in the prespecified order.

#### 9.6.5.2 Exploratory Endpoint Analysis

HAQ-DI score, HAQ pain and health scores, tophus size (longest axis), urate deposition volume, swollen/tender joint counts, physician global assessment score, and mean sUA will be summarized at baseline and each visit with descriptive statistics. Changes from baseline for these parameters to each visit and overall will be analyzed with a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model with a term for baseline score, tophi presence at baseline (except for analyses of tophi), and factors of treatment group, visit, and visit by treatment group interaction.

The proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria is defined as 20/50/70% improvement in 4 of the 5 components (TJC, SJC, HAQ pain, HAQ health, and tophus area). The proportion of subjects with improvement will be summarized and the difference between treatment groups analyzed with a CMH test. P-values for exploratory endpoints will be provided for descriptive purposes only, and treatment effects with corresponding two-sided 95% confidence intervals will be provided.

### 9.6.6 Pharmacokinetic and Anti-drug Antibody Analysis

Concentrations for pegloticase and MTX polyglutamate (as appropriate) will be summarized using descriptive statistics for the PK population. Details will be provided in a separate PK analysis plan.

Incidence of anti-drug antibodies and titer levels will be summarized.

### 9.6.7 Safety Analysis

Treatment-emergent AEs (TEAEs) during the MTX Tolerability Assessment Period and Run-In Period are defined as events with an onset date on or after the first dose of MTX through the first pegloticase infusion, or 30 days after the last dose of MTX for subjects who do not receive pegloticase. TEAEs during the Pegloticase + IMM Period are defined as events that occur after the start of the first pegloticase infusion through 30 days after the last dose of pegloticase and/or MTX or placebo for MTX (whichever is later). TEAEs that occur during the MTX Tolerability Assessment Period prior to randomization (Weeks -6 to -4) will be summarized separately for the MTX population. TEAEs will be summarized for the safety population separately for the Run-In Period (after randomization at Week -4 to Day 1) by treatment group (MTX and placebo for MTX) and the Pegloticase + IMM Period by treatment group (pegloticase with MTX and pegloticase with placebo for MTX), and overall (after randomization through 30 days after the last dose of treatment) by treatment group (MTX and placebo for MTX). AEs that occur more than 30 days after the last dose of pegloticase and/or MTX or placebo for MTX through the 6 month follow-up visit will also be summarized.

The number and percentage of subjects experiencing AEs will be summarized by system organ class and preferred term. Summaries by maximum severity and relationship to MTX and/or pegloticase will also be provided. SAEs and AEs leading to discontinuation of MTX and/or pegloticase will be presented by system organ class and preferred term.

The proportion of subjects with SAEs and each AESI will be summarized by treatment group. A Fisher's exact test will be performed to evaluate the difference in proportions between pegloticase with MTX vs. pegloticase with placebo for MTX. The proportion of subjects experiencing an SAE and each AESI will be summarized for each treatment group, along with the treatment difference in proportions, corresponding 95% CI for the treatment difference and p-value.

Laboratory test results, including urine albumin:creatinine ratio, will be summarized by study visit and change from baseline. Shift tables for laboratory parameters by Common Terminology Criteria for Adverse Events grade will be presented. Laboratory test results will also be classified relative to the normal reference range (normal, low, or high).

Vital signs, including blood pressure, respiratory rate, temperature, and heart rate, will be summarized by study visit and change from baseline.

Prior and concomitant medications will be summarized and/or included in the data listings.

Data for the MTX Tolerability Assessment Period, Run-in Period and Pegloticase + IMM Period will be summarized separately, and for the Run-in and Pegloticase + IMM periods combined, where applicable.

### 9.6.8 Interim Analyses

An interim analysis will be undertaken when all subjects have reached the Week 24 visit. An independent DMC will be convened to oversee and interpret this analysis to assess the primary

endpoint of maintaining sUA <6 mg/dL at least 80% of the time during Month 6 (Weeks 20, 21, 22, 23 and 24) comparing pegloticase with MTX to pegloticase with placebo for MTX, as well as to assess the safety of the co-administration of pegloticase with MTX based on all accrued data at that time. The DMC will recommend unblinding the Sponsor, stopping the study, or continuing without change at the time of the interim analysis, based on pre-defined criteria that will be outlined in the DMC charter. In the event of a highly clinically compelling increase in response rates with pegloticase with MTX vs pegloticase with placebo for MTX, and in the absence of any unexpected safety findings, the Sponsor may become unblinded for full data analysis. Subjects would continue on study through Week 52, with investigators and subjects remaining blinded. Clear parameters to guide decision criteria will be pre-specified in advance. Upon all subjects reaching Week 52, a final analysis would be completed in which the secondary endpoints would be tested, including maintaining sUA <6 mg/dL at least 80% of the time during Month 9, maintaining sUA <6 mg/dL at least 80% of the time during Month 12, and proportion of subjects with complete resolution of at least one tophus by digital photography through Week 24. Additional safety data accrued would also be summarized.

Criteria would also established and pre-specified for the DMC to recommend study discontinuation due to futility or an unexpected safety risk. An interim analysis for futility maybe completed earlier on the basis of the MIRROR Open-Label study results. At the futility analysis there will be no opportunity to conclude a benefit of MTX and therefore there will be no adjustment to the Type I error.

If none of the above scenarios are established, the study would continue and the Sponsor would remain blinded until all subjects reach Week 52.

### 9.6.9 Sample Size and Power Considerations

The response rate during Month 6 on pegloticase 8 mg every 2 weeks was 43% for the phase 3 studies. A sample size of 135 subjects (90 subjects randomized to receive pegloticase with MTX, 45 subjects randomized to receive pegloticase with placebo for MTX) provides 88% power at the 2-sided alpha=0.05 level to detect a difference of 28% (71% response rate for pegloticase with MTX vs. 43% for pegloticase with placebo for MTX).

## 9.7 Changes in the Conduct of the Study

If any modifications in the experimental design, dosages, parameters, subject selection, or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before any such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approved from the appropriate IRB.

All protocol deviations and the reasons for such deviations **must** be documented in the eCRF. In the event of a major protocol deviation, the Investigator and Sponsor's Medical Monitor will determine whether the subject should continue to participate in the study.

The Sponsor has a legal responsibility to report fully to regulatory authorities all results of administration of investigational drugs to humans. No investigational procedures other than those

described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB and Sponsor.

# 10 SOURCE DOCUMENTATION AND INVESTIGATOR FILES

The Investigator must maintain adequate and accurate records to document fully the conduct of the study and to ensure that study data can be subsequently verified. These documents should be classified in 2 separate categories: (1) Investigator study file and (2) subject clinical source documents that corroborate data collected in the eCRFs. Subject clinical source documents would include, as applicable, original hospital/clinic subject records; physicians' and nurses' notes; appointment book; original laboratory, ECG, electroencephalogram, radiology, pathology, and special assessment reports; dispensing records; signed ICFs; consultant letters; and subject screening and enrollment logs.

In order to comply with regulatory requirements, it is the policy of the Sponsor that, at a minimum, the following be documented in source documents at the study center:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify that the subject meets protocol entry criteria.
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed progress notes).
- Progress notes for each subject visit (each dated and signed).
- Records of each study visit including each study assessment and the identity of the staff member performing the assessment.
- Study drug dispensing and return.
- Review by the Investigator or qualified personnel on the 1572 of laboratory test results.
- AEs (start and stop date, description, action taken, and resolution).
- Investigator or sub-investigator's signed assessment of AEs.
- Concomitant medications (start and stop dates, reason for use).
- Condition of subject upon completion of, or premature withdrawal from, the study.

# 11 CASE REPORT FORMS

An eCRF is required for every subject who signs the ICF. Required data must be entered on the eCRF within the required time period, which will be outlined within each site agreement, after data collection or the availability of test results. Separate source records are required to support all eCRF entries. Data captured on the eCRF, and requested anonymized copies of supporting documents, will be transferred to the Sponsor at study completion.

The Investigator will ensure that the eCRFs are accurate, complete, legible, and timely, and will review and provide an electronic signature for the eCRF according to the standard operating procedure of the Data Management System. Final eCRFs will be provided to the Investigator and Sponsor by Data Management.

# 12 STUDY MONITORING

The Investigator will ensure that the study is conducted in accordance with all regulations governing the protection of human subjects. The Investigator will adhere to the basic principles of GCP as outlined in Title 21 of the CFR, Part 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, "Protection of Human Subjects"; 21 CFR, Part 56, "Institutional Review Boards"; 21 CFR, Part 54 "Financial Disclosure by Clinical Investigators"; and the ICH guideline entitled "Good Clinical Practice: Consolidated Guidance." Additionally, this study will be conducted in compliance with the Declaration of Helsinki and with all local laws and regulations.

The Investigator will ensure that all work and services described in, or associated with, this protocol are conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice. The Investigator will provide copies of the study protocol and Investigator's Brochure to all Sub-Investigators, pharmacists, and other staff responsible for study conduct.

All aspects of the study will be monitored by qualified individuals designated by the Sponsor. The Sponsor will ensure that the study is monitored adequately in accordance with GCP guidelines.

Prior to initiation of the study, the Sponsor's representatives will review with study center personnel information regarding the investigational drug, protocol requirements, monitoring requirements, and reporting of SAEs.

At intervals during the study, as well as after the completion of subject enrollment, the study center will be monitored by the Sponsor or designee for compliance. During these visits, the monitor will discuss study progress, verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on the eCRF (source data verification); oversee the resolution of outstanding data discrepancies, and check on various aspects of study conduct (e.g., drug accountability, sample storage). The Investigator agrees to allow monitors access to the clinical supplies, dispensing and storage areas, and clinical records of the study subjects, and, if requested, agrees to assist the monitors. The Investigator must cooperate with the monitors to ensure that any problems detected in the course of these monitoring visits are resolved.

A secondary audit may be conducted by Quality Assurance designated by the Sponsor. The Investigator will be informed if this is to take place and advised as to the nature of the audit. Representatives of the United States FDA and/or representatives of other regulatory authorities may also conduct an inspection of the study at the investigative site. If informed of such an inspection, the Investigator should notify the Sponsor immediately.

Every effort will be made to maintain the anonymity and confidentiality of subjects participating in this clinical study. However, because of the investigational nature of this treatment, the Investigator agrees to allow representatives of the Sponsor, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and to

have direct access to inspect, for purposes of verification, the hospital or clinical records of all subjects enrolled in this study. A statement to this effect should be included in the ICF.

# 13 DATA MANAGEMENT

Data will be entered into a clinical database, as specified in the Data Management Plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. Data will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be communicated to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

The coding of an AE, medical history and concomitant medication terms will be performed by the Sponsor or designated vendor and reviewed and approved by the Sponsor. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) and AE/medical history/surgery/non drug therapy terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

# 14 RETENTION OF RECORDS

No study documents at the study site should be destroyed without prior written agreement between the Sponsor and the Investigator. All subjects' medical records, the Investigator's copy of the eCRF, other supporting data, records of drug dispensing and accountability, signed ICFs, IRB correspondence, and correspondence with the Sponsor must be kept by the Investigator for at least 2 years and/or as required by the local law following the date of the last approval of a marketing application in an ICH region (including the United States) and until there are no pending or contemplated marketing applications in any other ICH region. If an application is not filed or not approved for the indication under study, all study-related files must be retained for at least 2 years and for a period in compliance with all federal, state, and local regulations. The Sponsor must be notified prior to the disposal of any study-related files. If the Investigator leaves the practice or institution during the required retention period, it is important that arrangements be made for continued record retention. In that event, the records generally will be retained at the institution at which the study was conducted.

# 15 PUBLICATION

To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts, and electronic communications), as detailed in the Clinical Trial Agreement.

# 16 REFERENCES

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# 17 APPENDICES

## 17.1 Administrative Appendix

This appendix provides names and contact information for the study administrative structure. The IRB must be notified of changes that are made to this section, but IRB review or approval of these changes is not required. Changes made in this section will be dated but will not be assigned a protocol amendment number.

| | |
|---|---|
| Medical Monitor | Barry Crittenden, MD<br>Horizon Pharma USA, Inc.<br>2000 Sierra Point Parkway, Suite 400<br>Brisbane, CA 94005<br>Mobile telephone number: 310-351-5882<br>Fax number: 224-383-3001<br>Email: BCrittenden@horizonpharma.com |
| Sponsor Representative | Molly Weiss<br>Senior Clinical Project Manager, Clinical Operations<br>Horizon Pharma USA, Inc.<br>150 S. Saunders Road<br>Lake Forest, IL 60045<br>Mobile telephone number: 847-924-8152<br>Fax number: 224-383-3001<br>Email: MWeiss2@horizonpharma.com |
| Sponsor Contact for Serious Adverse Event Reporting | spm2<br>Fax number: 800-860-7836<br>Email: clinicalsafety@horizonpharma.com |
| 24-hour Phone Contact for Safety Coverage | Med Communications<br>Phone number: 855-479-6742 |

## 17.2 Health Assessment Questionnaire (Disability Index, Pain and Health Scales)

**The STANFORD HEALTH ASSESSMENT QUESTIONNAIRE©**
**Stanford University School of Medicine, Division of Immunology & Rheumatology**

**HAQ Disability Index:**
In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

**Please check the response which best describes your usual abilities OVER THE PAST WEEK:**

| | Without ANY difficulty[0] | With SOME difficulty[1] | With MUCH difficulty[2] | UNABLE to do[3] |
|---|---|---|---|---|
| **DRESSING & GROOMING** | | | | |
| Are you able to: | | | | |
| -Dress yourself, including tying shoelaces and doing buttons? | ☐ | ☐ | ☐ | ☐ |
| -Shampoo your hair? | ☐ | ☐ | ☐ | ☐ |
| **ARISING** | | | | |
| Are you able to: | | | | |
| -Stand up from a straight chair? | ☐ | ☐ | ☐ | ☐ |
| -Get in and out of bed? | ☐ | ☐ | ☐ | ☐ |
| **EATING** | | | | |
| Are you able to: | | | | |
| -Cut your meat? | ☐ | ☐ | ☐ | ☐ |
| -Lift a full cup or glass to your mouth? | ☐ | ☐ | ☐ | ☐ |
| -Open a new milk carton? | ☐ | ☐ | ☐ | ☐ |
| **WALKING** | | | | |
| Are you able to: | | | | |
| -Walk outdoors on flat ground? | ☐ | ☐ | ☐ | ☐ |
| -Climb up five steps? | ☐ | ☐ | ☐ | ☐ |

**Please check any AIDS OR DEVICES that you usually use for any of these activities:**

- ☐ Cane
- ☐ Walker
- ☐ Crutches
- ☐ Wheelchair
- ☐ Devices used for dressing (button hook, zipper pul long-handled shoe horn, etc.)
- ☐ Built up or special utensils
- ☐ Special or built up chair
- ☐ Other (Specify:_____)

**Please check any categories for which you usually need HELP FROM ANOTHER PERSON:**

- ☐ Dressing and Grooming
- ☐ Arising
- ☐ Eating
- ☐ Walking

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

| | Without ANY difficulty [0] | With SOME difficulty [1] | With MUCH difficulty [2] | UNABLE to do [3] |
|---|---|---|---|---|
| **HYGIENE** | | | | |
| Are you able to: | | | | |
| -Wash and dry your body? | ☐ | ☐ | ☐ | ☐ |
| -Take a tub bath? | ☐ | ☐ | ☐ | ☐ |
| -Get on and off the toilet? | ☐ | ☐ | ☐ | ☐ |
| **REACH** | | | | |
| Are you able to: | | | | |
| -Reach and get down a 5-pound object (such as a bag of sugar) from just above your head? | ☐ | ☐ | ☐ | ☐ |
| -Bend down to pick up clothing from the floor? | ☐ | ☐ | ☐ | ☐ |
| **GRIP** | | | | |
| Are you able to: | | | | |
| -Open car doors? | ☐ | ☐ | ☐ | ☐ |
| -Open jars which have been previously opened? | ☐ | ☐ | ☐ | ☐ |
| -Turn faucets on and off? | ☐ | ☐ | ☐ | ☐ |
| **ACTIVITIES** | | | | |
| Are you able to: | | | | |
| -Run errands and shop? | ☐ | ☐ | ☐ | ☐ |
| -Get in and out of a car? | ☐ | ☐ | ☐ | ☐ |
| -Do chores such as vacuuming or yardwork | ☐ | ☐ | ☐ | ☐ |

**Please check any AIDS OR DEVICES that you usually use for any of these activities:**

- ☐ Raised toilet seat
- ☐ Bathtub seat
- ☐ Jar opener (for jars previously opened)
- ☐ Bathtub bar
- ☐ Long-handled appliances for reach
- ☐ Long-handled appliances in bathroom
- ☐ Other (Specify:_____)

**Please check any categories for which you usually need HELP FROM ANOTHER PERSON:**

- ☐ Hygiene
- ☐ Reach
- ☐ Gripping and opening things
- ☐ Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.
**How much pain have you had because of your illness IN THE PAST WEEK:**

PLACE A VERTICAL (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN

**No Pain** — **Severe Pain**

|_____|

**0** — **100**

**Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line.**

**Very Well** — **Very Poor**

|_____|

**0** — **100**

## 17.3 Physician Global Assessment

PHYSICIAN GLOBAL ASSESSMENT

"Considering this patient's overall health related to gout, rate their gout overall by circling a number from 0 – 10 on the scale below"

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Excellent Health | | | | | | | | | | Very Poor Health |