Study: HZNP-KRY-201

NCT#: 03635957

TITLE:

Protocol
A Multicenter, Efficacy and Safety Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled GOut Receiving
KRYSTEXXA® (pegloticase) (MIRROR Open-Label [OL])

Date of Document:

Protocol: 01 April 2020

150 S. Saunders Road, Lake Forest, IL 60045

CLINICAL STUDY PROTOCOL FOR KRYSTEXXA

IND: 010122

Protocol Number: HZNP-KRY-201

Version 3.0, Amendment 2, Administrative Change 1

A Multicenter, Efficacy and Safety Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled GOut Receiving KRYSTEXXA® (pegloticase) (MIRROR Open-Label [OL])

Short Title: MIRROR OL

Effective Date: 01 April 2020

Sponsor:
Horizon Therapeutics Ireland DAC
1 Burlington Road
Connaught House, 1st Floor
Dublin Ireland
D04 C5Y6

PROTOCOL

1 TITLE PAGE

Study Title:	A 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 Open-Label [OL])
Protocol Number:	HZNP-KRY-201
Version:	3.0, Amendment 2, Administrative Change 1
Investigational Products:	KRYSTEXXA (recombinant modified mammalian urate oxidase [uricase]); methotrexate (MTX)
Indication:	Chronic gout in adult patients refractory to conventional therapy
Sponsor:	Horizon Therapeutics Ireland DAC 1 Burlington Road Connaught House, 1st Floor Dublin Ireland D04 C5Y6
Development Phase:	4
Sponsor's Responsible Medical Officer:	[redacted] Horizon Therapeutics USA, Inc. 150 S. Saunders Road Lake Forest, IL 60045
Sponsor Signatory:	[redacted] Horizon Therapeutics USA, Inc. 150 S. Saunders Road Lake Forest, IL 60045
Approval Date:	**01 April 2020**

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: [redacted]
Email: [redacted]

SPONSOR SIGNATURE PAGE

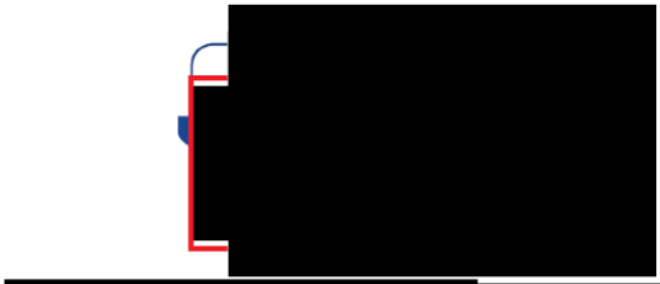
Protocol Number: HZNP-KRY-201

Version: 3.0, Amendment 2, Administrative Change 1

Protocol Title: A 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 Open-Label [OL])

Version Date: 01 April 2020

Approved by:



Date

Horizon Therapeutics USA, Inc.

Date

Horizon Therapeutics USA, Inc.

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-201

Version: 3.0, Amendment 2, Administrative Change 1

Protocol Title: A 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 Open-Label [OL])

Version Date: 01 April 2020

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
Study Center
Address
City State Country

Date

SUMMARY TABLE OF CHANGES

SUMMARY TABLE OF CHANGES

SUMMARY TABLE OF CHANGES
Protocol Version 1.0, Original (27 July 2018) to
Protocol Version 2.0, Amendment 1 (16 August 2018)
Protocol Version 3.0, Amendment 2 (17 April 2019)
Protocol Version 3.0, Amendment 2, Administrative Change 1 (01 April 2020)

The Administrative Change includes the removal of the Scientific Advisory Committee and an update to the Medical Monitor information, Sponsor entity and company name change, clarification of Adverse Event follow-up language and safety reporting e-mail, correction of typographical errors and corrections and updates to references section . Track changes version of the Protocol Version 3.0, Amendment 2, Administrative Change 1 can be provided on request.

2 SYNOPSIS

Protocol Title: A 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 Open-Label)	
Protocol Number: HZNP-KRY-201	**Phase**: 4
Protocol Version: 3.0, Amendment 2, Administrative Change 1	
Test Drugs: KRYSTEXXA; methotrexate (MTX)	**Indication**: Chronic gout in adult patients refractory to conventional therapy
Number and Country of Study Sites: Approximately 8 study centers in the United States	

Objectives:
The overall objective of the study is to assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of the concomitant use of pegloticase with MTX to enhance the response rate seen with pegloticase alone in adults with uncontrolled gout.

Primary Objective

The primary objective is to estimate the response rate during Month 6 (Weeks 20, 22, 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 in subjects receiving pegloticase with MTX.

Secondary Objectives

- Estimate 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 in subjects receiving pegloticase with MTX.
- Estimate 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, 22 and 24) combined in subjects receiving pegloticase with MTX.
- Estimate the 5 mg/dL response rate during Month 3, during Month 6, and Overall (Months 3 and 6 combined), as measured by the sustained normalization of sUA to <5 mg/dL for at least 80% of the time in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in sUA in subjects receiving pegloticase with MTX.

Exploratory Objectives

- Estimate 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 in subjects receiving pegloticase with MTX.
- Estimate 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 in subjects receiving pegloticase with MTX.
- Estimate the 5 mg/dL response rate during Month 9 (Weeks 32, 34 and 36), as measured by the sustained normalization of sUA to <5 mg/dL for at least 80% of the time during Month 9 in subjects receiving pegloticase with MTX.
- Estimate the 5 mg/dL response rate during Month 12 (Weeks 48, 50 and 52), as measured by the sustained normalization of sUA to <5 mg/dL for at least 80% of the time during Month 12 in subjects receiving pegloticase with MTX.
- Estimate the time to first sUA > 6 mg/dL in subjects receiving pegloticase with MTX.
- Estimate the time to two consecutive sUAs > 6 mg/dL (stopping rule) in subjects receiving pegloticase with MTX.

- Estimate the mean change from baseline to Week 24, 36 and 52 in urate volume and gout erosions using dual-energy computed tomography (DECT) scan of the hands and feet in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline in number of joints affected by tophi in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in tender joint count (68-point scale) in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in swollen joint count (66-point scale) in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in the Health Assessment Questionnaire – Disability Index (HAQ-DI) in subjects receiving pegloticase with MTX
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in the HAQ Pain score in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in the HAQ Health score in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in patient global assessment of gout in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in physician global assessment of gout in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in subject assessment of average, least, and worst joint pain in subjects receiving pegloticase with MTX.
- Estimate the proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36, and 52 in subjects receiving pegloticase with MTX.
- Assess the PK of pegloticase in subjects receiving concomitant MTX
- Assess the incidence of anti-PEG and anti-Uricase IgG antibodies

Safety and Tolerability Objectives

- Assess the incidence of infusion reactions (IRs), anaphylaxis, gout flares, cardiovascular events, and the adverse event (AE)/serious AE profile overall and potentially attributed to the combination of pegloticase and MTX.

Study Design

This is a multicenter, open-label, efficacy and safety study of pegloticase with MTX in adult subjects with uncontrolled gout.

The study design will include: 1) up to a 2-week Screening Period (screening should be complete within 2 weeks prior to Week -4), 2) a 4-week MTX Run-in Period; 3) a 52-week Pegloticase + IMM (Pegloticase + MTX) Period 4) a Safety Follow-up (Phone/Email/Site Visit) and 5) a 3 and 6 month Post Treatment Follow-up.

All subjects who meet eligibility criteria at Screening will begin oral MTX at a dose of 15 mg weekly for 4 weeks prior to the first dose of pegloticase.

Subjects will also take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) continuing until prior to the Week 52 Visit. Subjects must be able to tolerate MTX at a dose of 15 mg during the 4 week MTX Run-in Period (prior to Day 1) to be eligible to participate in the Pegloticase + IMM Period. Subjects who are unable to tolerate MTX at a dose of 15 mg during the MTX Run-in Period will be considered screen failures.

Subjects who take at least one dose of MTX 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 after the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. For those subjects who take at least one dose of MTX and who are non-vasectomized males an inquiry will be conducted at the Post-Treatment 3 month follow-up visit (or 3 months after the subject's last

dose of MTX) after MTX discontinuation regarding partner pregnancy.

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 (60 mg or 180 mg orally based on the Principal Investigator's discretion) will be taken the day before each infusion; fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) given over the infusion duration 10-30 minutes (recommended) or hydrocortisone (200 mg IV) will be administered 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.

During the Pegloticase + IMM Period, subjects will be instructed to take 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 must be taken ≥60 minutes prior to each pegloticase infusion

After Day 1, if a subject becomes unable to tolerate 15 mg of MTX, the MTX dose may be reduced and/or discontinued, and the subject may remain in the study.

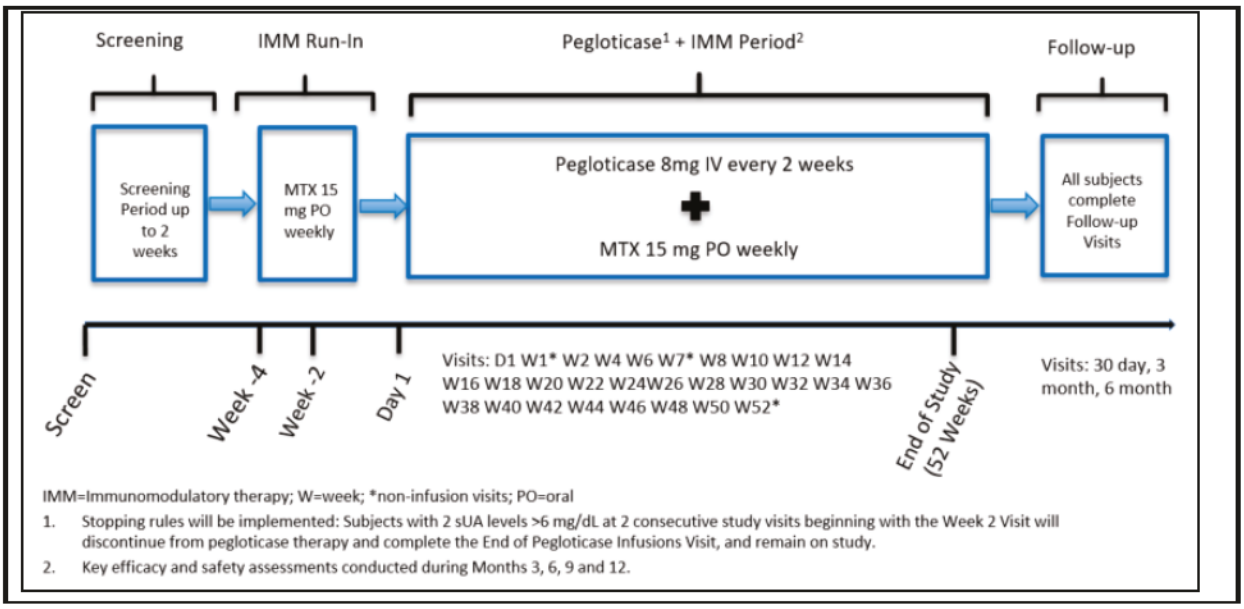
The Investigator will review the clinical status and individual subject treatment goals at Week 24, and the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of study/Early Termination Visit.

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 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 ≥6 mg/dL and an inability to maintain sUA <6 mg/dL on other urate-lowering therapy, intolerable side effects associated with current urate-lowering therapy, and/or functionally limiting tophaceous deposits (including those detected clinically or by DECT imaging).

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 to ≤65 years of age.
4. 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 the Screening and MTX Run-in Period; 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 -4 (start of MTX dosing) and continue for 30 days after the last dose of pegloticase, or at least one ovulatory cycle after the last dose of MTX (whichever is the longest duration after the last dose of pegloticase or 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.
5. Men who are not vasectomized must agree to not impregnate their female partner during the study and for at least 3 months after the last dose of MTX.
6. Hyperuricemia at the Screening, Week -4, or Week -2 Visit of the Screening or Run-in Period, as documented by sUA ≥6 mg/dL.
7. Uncontrolled gout, defined as meeting the following criteria:
   - sUA ≥6 mg/dL prior to entry into the pegloticase +IMM Period (any laboratory tests during screening up to and including during the MTX Run-in Period) and at least 1 of the following:
     - inability to maintain sUA <6 mg/dL on other urate-lowering therapy
     - intolerable side effects associated with current urate-lowering therapy
     - functionally limiting tophaceous deposits (including those detected clinically or by DECT imaging)
8. Able to tolerate MTX 15 mg for 4 weeks during the MTX Run-in Period prior to the first dose of pegloticase.

Exclusion Criteria:

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

1. Weight >160 kg (352 pounds).
2. Any serious acute bacterial infection, unless treated and completely resolved with antibiotics at least 2 weeks prior to the Week -4 Visit of the MTX Run-in Period.
3. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis.
4. Current immunocompromised condition, including current or chronic treatment with systemic immunosuppressive agents, including prednisone >10 mg/day or equivalent dose of other corticosteroid.
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. Human Immunodeficiency Virus (HIV) positivity (tested at Screening Visit).
9. Glucose-6-phosphate dehydrogenase deficiency (tested at the Screening Visit).
10. Severe chronic renal impairment (glomerular filtration rate <25 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) at the end of the Screening and MTX Run-in Period.
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 (KRYSTEXXA®), 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 -4 or plans to take an investigational drug during the study.
18. Current liver disease, as determined by alanine transaminase or aspartate transaminase levels >3 times upper limit of normal at the Screening Visit.
19. Currently receiving systemic or radiologic treatment for ongoing cancer, excluding non-melanoma skin cancer.
20. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix.
21. Uncontrolled hyperglycemia with a plasma glucose value >240 mg/dL at screening that is not subsequently controlled by the end of the Screening/MTX Run-in Period.
22. Diagnosis of osteomyelitis.
23. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
24. 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.
25. Alcohol use in excess of 3 alcoholic beverages per week.
26. Currently receiving allopurinol and unable to discontinue medication 7 days prior to MTX dosing at Week -4 and unable to discontinue treatment during the duration of the study.

Dose Regimen/Route of Administration:

MTX:

During the MTX Run-in Period, which begins 4 weeks prior to the first dose of pegloticase, subjects will take oral MTX at a dose of 15 mg weekly.

Subjects will be instructed to take MTX weekly on the same day each week (if dosing more frequently than once in a day (ie. BID, TID), the total MTX dose should be taken within 24 hours, preferably the same calendar day) and record the date and time of each dose in the dosing calendar.

During the MTX 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. Investigators may choose to have subjects take the weekly dose divided over the day (ie. BID, TID). The total MTX dose should be taken within 24 hours, preferably the same calendar day each week, with the date and time of each MTX dose recorded in the dosing calendar.

During the Pegloticase + IMM Period, MTX should be taken 1 to 3 days prior to the pegloticase infusion and one additional weekly dose after the last infusion (at Week 51) for subjects who have not stopped pegloticase due to sUA stopping rules. If a subject is not able to take the MTX 1 to 3 days prior to the pegloticase infusion, MTX must be taken ≥60 minutes prior to the pegloticase infusion.

During the Pegloticase + IMM Period, if a subject becomes unable to tolerate the MTX the dosage may be decreased.

Subjects will also take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the Week 52 Visit.

Pegloticase:

All subjects who meet the inclusion/exclusion criteria and tolerate oral MTX 15 mg weekly during the MTX 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 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 and 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 will be provided to subjects as a commercially available generic.

Duration of Treatment and Follow-up:

Screening: Completed within 2 weeks prior to the Week -4 visit

MTX Run-in Period (Week -4 through Day 1): Includes 4 weeks of MTX weekly dosing

Pegloticase + IMM Period (Day 1 through Week 52): MTX dosed weekly and 50 weeks of pegloticase infusions visits every 2 weeks); Non-infusion visits at Weeks 1, 7 and 52.

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.

Week 52/End-of-study/Early Termination Visit: Week 52 or earlier if the subject withdraws consent to participate in the study.

Safety Follow-up Visits: All subjects will receive a safety follow-up phone call/e-mail/visit approximately 30 days after the last dose of pegloticase/MTX to assess if any SAE's have occurred. Subjects who receive at least one dose of MTX and are females of childbearing potential, will receive a safety follow-up phone call/e-mail/Site Visit approximately 30 days after the last dose of MTX to verify at least one ovulatory cycle has occurred after the last dose of 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/Site Visit inquiry will be conducted 3 months after MTX discontinuation regarding partner pregnancy (inquiry can occur during the 3 month Post Treatment Follow-up).

3 and 6 Month Post Treatment Follow-up Visits: 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:

Efficacy will be assessed by sUA levels, tender and swollen joint counts, patient and physician global assessments of gout, joint pain, and DECT.

Quality of life will be assessed using the HAQ.

The PK of pegloticase and pegloticase immunogenicity as assessed by the incidence of anti-PEG and anti-uricase IgG antibodies will be assessed at specified time points.

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:

Individual Subject 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 discontinue treatment and remain in the study.

Statistical Analyses:

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of Month 6 (Weeks 20, 22, 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 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, 22 and 24) combined
- The proportion of 5 mg/dL responders during Month 3, Month 6, and overall (Months 3 and 6 combined), defined as subjects achieving and maintaining sUA < 5 mg/dL for at least 80% of the time during each timepoint.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in sUA.

Exploratory Efficacy Endpoints

- 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.
- 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.
- The proportion of Month 9 (Weeks 32, 34 and 36) 5 mg/dL responders, defined as subjects achieving and maintaining sUA <5 mg/dL for at least 80% of the time during Month 9.
- The proportion of Month 12 (Weeks 48, 50 and 52) 5 mg/dL responders, defined as subjects achieving and maintaining sUA <5 mg/dL for at least 80% of the time during Month 12.
- The time to first sUA >6 mg/dL.
- The time to two consecutive sUAs >6 mg/dL (stopping rule) in subjects receiving pegloticase with MTX.
- The mean change from baseline to Weeks 24, 36, and 52 in urate volume and bone erosions due to gout using DECT.
- The mean change from baseline in number of joints affected by tophi.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in tender joint count (68-point scale).
- The mean change from baseline to Weeks 14, 24, 36, and 52 in swollen joint count (66-point scale).
- The mean change from baseline to Weeks 14, 24, 36, and 52 in HAQ-DI.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in HAQ Pain score.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in HAQ Health score.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in patient global assessment of gout.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in physician global assessment of gout.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in subject assessment of average, least, and worst joint pain.
- The proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36, and 52.

Pharmacokinetic and Anti-drug Antibody Endpoints

- PK of pegloticase.
- Incidence of anti-PEG and anti-Uricase IgG antibodies.

Safety and Tolerability Endpoints

- Incidence of IRs, anaphylaxis, gout flares, cardiovascular events, and the AE/serious AE profile

Statistical Analysis on Efficacy Parameters

The efficacy analysis will be performed using the modified intention-to-treat (mITT) population, defined as all enrolled subjects who received ≥1 dose of pegloticase. The proportion of Month 6 responders will be summarized, along with a 95% confidence interval for the proportion. The proportion of Month 3 and overall (Months 3 and 6 combined) responders will be analyzed similarly.

A subject will be declared a non-responder if the subject had sUA level > 6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit. In addition, a subject who withdraws from study treatment for any reason after the first dose of pegloticase in the Pegloticase + IMM Period and prior to Month 6 (for the primary endpoint) or Month 3 (for the secondary endpoint) will be considered a non-responder if sUA values are not collected at the planned time points.

Swollen/tender joint counts, HAQ scores, patient and physician global assessment scores, subject assessment of joint pain scores, and mean sUA changes from baseline and values at baseline and each visit will be summarized with descriptive statistics. The proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria will be summarized. For subjects with DECT scans, changes from baseline and values at Weeks 24, 36 and 52 for urate volume will be summarized with descriptive statistics.

Sample Size Estimate:

A sample size of approximately 12-16 subjects is planned for this study. The primary efficacy endpoint, the proportion of subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6 (Weeks 20, 22, and 24) of the Pegloticase + IMM Period, will be demonstrated to be statistically greater than 43.5% (proportion of responders during Month 6 in phase 3 studies), according to a exact test for proportions with a 5% type I error, if at least 10/13 (77%) responders are observed; in that case, the lower bound of a 95% confidence interval for the proportion of responders will be about 46%.

2.1 Schedule of Assessments

	Screening[1]/ MTX Run-in Period[2]			Pegloticase + IMM Period[3] Day 1 through Week 24														
	Screening Visit [4]	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 1 (±1 d)	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 7 (±1 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 22 (±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																	
Enrollment				X														
Demographic data	X																	
Inclusion/exclusion criteria	X	X	X	X														
Medical/surgical history[5]	X	X																
Medication/substance use history[6]	X	X	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
Electrocardiogram[9]				X														
HIV antibody screening	X																	
AE/SAE assessment[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening[1]/ MTX Run-in Period[2]			Pegloticase + IMM Period[3] Day 1 through Week 24														
	Screening Visit [4]	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 1 (±1 d)	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 7 (±1 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 22 (±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**
Concomitant medications				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
HAQ	X	X		X									X					X
Patient global assessment	X	X		X									X					X
Physician global assessment	X	X		X									X					X
Joint pain assessment	X	X		X									X					X
DECT[11]				X														X
Tophi Assessment	X																	X
MTX dosing calendar		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MTX dispensed[12]		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X
MTX dosing[13]		Once weekly from Week -4 to the week 51, one week after the Week 50 Visit, inclusive																
Gout prophylaxis Rxs filled[14]		Rxs filled as needed																

	Screening[1]/ MTX Run-in Period[2]			Pegloticase + IMM Period[3] Day 1 through Week 24														
	Screening Visit [4]	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 1 (±1 d)	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 7 (±1 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 22 (±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**
Fexofenadine Rx filled[15]		Rx filled as needed																
Folic acid Rx filled[16]		Rx filled as needed																
MTX compliance/ reconciliation			X	X		X	X	X		X	X	X	X	X	X	X	X	X
Infusion reaction prophylaxis[17]				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
Folic acid/gout flare prophylaxis compliance (Yes/No)			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
Pre-infusion MTX Polyglutamate sampling[18]				X			X			X							X	X
pegloticase PK sampling[19]				X	X	X	X	X	X	X	X		X		X		X	X
sUA[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X		X		X					X				X	X

	Screening[1]/ MTX Run-in Period[2]			Pegloticase + IMM Period[3] Day 1 through Week 24														
	Screening Visit [4]	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 1 (±1 d)	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 7 (±1 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 22 (±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**
Clinical chemistry	X	X	X	X		X		X					X				X	X
Spot urine collection	X	X	X	X		X		X					X				X	X
Antibody sample[21]				X	X	X	X	X	X	X	X		X		X		X	X
G6PD	X																	
Pregnancy test[22]	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X
Partner pregnancy[23]																		
Investigator assessment of clinical status[24]																		X

	Pegloticase + IMM Period[3] Week 26 through Week 50													End of Pegloticase Infusions Visit[25] (if applicable)	End of Study/ Early Termination	Safety Follow-up Phone/ Email Visit 30 Day	MTX Partner Pregnancy Follow-up	Post Treatment 3 and 6 month Follow-up[26]
	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 & 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
HAQ						X								X	X			X
Patient global assessment						X								X	X			X
Physician global assessment						X								X	X			X
Joint pain assessment						X								X	X			X
DECT[11]						X								X	X			

	Pegloticase + IMM Period[3] Week 26 through Week 50													End of Pegloticase Infusions Visit[25] (if applicable)	End of Study/ Early Termination	Safety Follow-up Phone/ Email Visit 30 Day	MTX Partner Pregnancy Follow-up	Post Treatment 3 and 6 month Follow-up[26]
	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 & 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**					
Tophi Assessment						X								X	X			X
Dispense MTX dosing calendar	X	X	X	X	X	X	X	X	X	X	X	X	X					
MTX dispensed[12]	X	X	X	X	X	X	X	X	X	X	X	X	X					
MTX dosing[13]	Once weekly from Week -4 to the week 51, one week after the Week 50 Visit, inclusive																	
Gout prophylaxis Rxs filled[14]	Rxs filled as needed																	
Fexofenadine Rx filled[15]	Rxs filled as needed																	
Folic acid Rx filled[16]	Rxs filled as needed																	
MTX compliance/ reconciliation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Infusion reaction prophylaxis[17]	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[25] (if applicable)	End of Study/ Early Termination	Safety Follow-up Phone/ Email Visit 30 Day	MTX Partner Pregnancy Follow-up	Post Treatment 3 and 6 month Follow-up[26]
	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 & 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					
Pre-infusion MTX Polyglutamate sampling[18]						X												
Pegloticase PK sampling[19]						X								X	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 sample[21]						X								X	X			X
Pregnancy test[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Partner pregnancy[23]																	X	

	Pegloticase + IMM Period[3] Week 26 through Week 50													End of Pegloticase Infusions Visit[25] (if applicable)	End of Study/ Early Termination	Safety Follow-up Phone/ Email Visit 30 Day	MTX Partner Pregnancy Follow-up	Post Treatment 3 and 6 month Follow-up[26]
	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 & 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**					
Investigator Assessment of Clinical Status[24]														X	X			

AE = adverse event; d = day(s); DECT = dual-energy computed tomography; G6PD = glucose-6-phosphate dehydrogenase; HAQ = Health Assessment Questionnaire; HIV = human immunodeficiency virus; 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 Period is inclusive of the MTX Run-in Period.
2. During the MTX Run-in Period, subjects will take oral MTX 15 mg weekly, which begins 4 weeks prior to the first dose of pegloticase. Subjects unable to tolerate 15 mg of MTX during the Run-in period will be considered screen failures.
3. It is recommended that before a subject begins the Pegloticase + IMM Period, he or she has been taking the per protocol standard gout flare prophylaxis regimen for ≥1 week prior to pegloticase infusion. During the Pegloticase + IMM Period subjects will continue taking MTX weekly inclusive of Week 51 (1 week after the last pegloticase infusion). Subjects will receive pegloticase infusions every 2 weeks Day 1 through Week 50.
4. The Week -6 Visit is designated the Screening Visit and can occur any time within 2 weeks prior to the first dose of MTX at Week -4.
5. The Investigator or designee will collect a complete gout history and other relevant medical/surgical history.
6. Medication history (i.e., prior medications) will include gout medications, starting at the time of diagnosis and up to (but not including) the Day 1 Visit; substance use history; History of all prior gout medications will be collected. History of non-gout medication use in the year prior to Screening will be collected.
7. A complete physical examination will be performed at the Screening Visit and will include assessments of for presence of tophi, as well as gout history and symptom severity. A targeted physical examination (includes heart, lungs and abdominal exam and exam for joint and skin evaluation and assessment of AEs) will be conducted based on potential risk for or occurrence of AEs at Week -4, Day 1, and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20, 24, 36, Week 52/End of Study/Early Termination and Post Treatment 3 and 6 month Follow-up Visits. Clinically significant findings from the targeted physical examinations will be recorded as AEs. At Weeks 24 and 36, Week 52/End of Study/Early Termination and Post Treatment 3 and 6 month Follow-up Visits, an assessment for presence of tophi will be conducted during the targeted physical examination.

8. 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 for at least 5 minutes and, for study visits during the Pegloticase + IMM Period, before the pegloticase infusion and any time after the end of the infusion, but prior to subject's discharge/release from the site. Weight should be measured in kilograms or pounds without shoes and recorded at Screening Visit; prior to pegloticase infusions on Day 1 and at the Week 8, 16, 24, 36, the End of Pegloticase Treatment, at the Week 52/End-of-study/Early Termination Visit and the Post Treatment 3 and 6 month follow-up visits. Height will be collected at the Screening Visit only.
9. Electrocardiogram should be completed prior to the pegloticase infusion at Day 1 Visit.
10. AEs/SAEs will be collected from signature of the ICF. Serious AEs will be captured/monitored at the Safety Follow-up Phone/Email/Site Visit 30 days after the last dose of MTX. At the Safety Follow-up Phone/Email/Site Visit, females of childbearing potential will be asked to confirm if ovulation has occurred since the last dose of MTX. If the subject had not ovulated, a urine pregnancy test will be required. AEs/SAEs will collected until the 6 month Post Treatment Follow-up Visit. For each AE, Investigators will be record if the event was possibly an infusion reaction or anaphylaxis and if so, will be prompted to complete additional CRFs.
11. For sites with DECT capability, 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.
12. MTX will be dispensed and brought back at each visit to check compliance. If subjects require a MTX dose reduction, the Investigator will prescribe the subject the number of tablets to take weekly. The updated number of tablets along with the date and time of each MTX dose should be recorded in the dosing calendar.
13. MTX should be taken 1 to 3 days prior to pegloticase infusion; however, if a subject does not do so, MTX must be taken ≥60 minutes prior to pegloticase infusion.
14. For gout prophylaxis, subjects are required to take 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 (60 mg or 180 mg orally based on the Principal Investigator's discretion) will be taken the day before each infusion; fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) given over the infusion duration 10-30 minutes (recommended) or hydrocortisone (200 mg IV) will be administered immediately prior to each infusion. given over the infusion duration 10-30 minutes will be administered immediately prior to each infusion.
15. For IR prophylaxis, fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) will be taken the day before each infusion.
16. Subjects will take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the Week 52/End of Study/Early Termination Visit during the Pegloticase + IMM Period.
17. Infusion reaction prophylaxis includes fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) administered the day before each infusion; fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) and acetaminophen (1000 mg orally) administered on the morning of each infusion; and methylprednisolone (125 mg IV) given over the infusion duration 10-30 minutes (recommended) or hydrocortisone (200 mg IV) will be administered immediately prior to each infusion. administered immediately prior to each infusion.
18. Blood samples will be collected prior to pegloticase infusion on Day 1 and at Weeks 4, 8, 22, 24 and 36 during the Pegloticase + IMM Period for MTX Polyglutamate levels.
19. For all subjects, serum samples for PK analysis will be collected prior to pegloticase infusion and after the end of infusion (prior to discharge) on Day 1 and at the Weeks 2, 4, 6, 8 and 36 Visits and prior to pegloticase infusion only at the Weeks 10, 14, 18, 22, 24; at the End of Pegloticase Infusions Visit (if applicable); and Week 52/End-of-Study/Early Termination Visit. Visits for frequent sampling of a subset of subjects who consent for additional non-infusion visit PK sampling (random, morning preferred) will occur at Week 1 and Week 7.
20. Serum samples for measurement of sUA levels will be collected at the Screening Visit (within 2 weeks prior to the first dose of MTX at Week -4), the Week -4 Visit (prior to the first dose of MTX), and the Week -2 Visit; within 48 hours prior to each pegloticase infusion (except on Day 1 when only 1 pre-infusion sample is required and will be drawn at the site just prior to the infusion); and after the end of each pegloticase infusion prior to discharge, from the Pegloticase + IMM Period through week 24 and at Weeks 32, 34, 36, 48 and 50; within 48 hours prior to each pegloticase infusion at Weeks 26, 28, 30, 38, 40, 42, 44 and 46 during the Pegloticase + IMM Period; and at the at the End of Pegloticase Infusions Visit (if applicable); at the Week 52/End of study/Early Termination Visit and Month 3 and Month 6 Visits. Visits for frequent sampling of a subset of subjects who consent for additional non-infusion visit PK sampling (random, morning preferred) will occur at Week 1 and Week 7. Two separate samples/tubes of

blood should be collected within 48 hours prior to the pegloticase infusion (except on Day1 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 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 classified as a non-responder and subjects will complete the End of Pegloticase Treatment Visit. The subject will continue on study (without treatment).

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, 4, 6, 8, 10, 14, 18, 22, 24, 36, if applicable the End of Pegloticase Infusions Visit and Week 52/End of Study/Early Termination Visits and at the 3 Month Post Treatment Visit. Visits for frequent sampling of a subset of subjects who consent for additional non-infusion visit PK sampling (random, morning preferred) will occur at Week 1 and Week 7. 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.
22. For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit. A urine pregnancy test will be performed at each visit until 30 days after the last 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/site visit it is determined that the subject has not ovulated since the last dose of MTX; a urine pregnancy test will be performed at all other indicated visits.
23. Subjects who are non-vasectomized males will be asked 3 months after MTX discontinuation regarding partner pregnancy. This will occur at a regulatory scheduled visit or by a separate phone/email/site visit.
24. The Investigator will review the clinical status of the subject at the Week 24 Visit and the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of study/Early Termination Visit.
25. 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 9.5.6.3 for details on visits and procedures.
26. Subjects will return to the site 3 months and 6 months following their final infusion for follow-up procedures.

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
CFR	Code of Federal Regulations
DECT	Dual energy computed tomography
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	nonsteroidal anti-inflammatory drug
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
sUA	serum uric acid
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 Therapeutics Ireland DAC (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, or designee 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 8 study centers in the United States, and the Principal Investigator is [redacted] at the [redacted] in [redacted] (Table 6.1). 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
Principal Investigator	[redacted]
Clinical drug supply and distribution	[redacted]
MTX Polyglutamate laboratory	[redacted]
Central safety laboratory	[redacted]
Data Management	[redacted]
Statistics	[redacted]

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]. Up to 400,000 persons (up to 5% of the estimated 8 million persons with gout) in the United States experience chronic symptoms of gout, despite trials of urate-lowering therapy. Gout, which is sometimes referred to as chronic refractory gout, 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.

KRYSTEXXA (pegloticase, a recombinant modified mammalian urate oxidase [uricase]), is approved by the United States FDA and the European Commission for use in patients with gout, at a dose of 8mg IV every two weeks. Pegloticase is efficacious in reducing sUA levels and improving clinical signs and symptoms of gout. Pegloticase provides medical benefits by lowering sUA and eliminating tophi in patients who currently have no therapeutic options. The pooled response rate for pegloticase 8 mg at 6 months is 42%, based on at least 80% of the sUA values being less than 6 at both the 3 month and 6 month time points, with placebo response rates of 0%, a difference that was clinically important and statically significant.

However, pegloticase has been associated with infusion reactions (IRs), including anaphylaxis. In Phase 3 studies, IRs occurred in 26% of subjects receiving pegloticase compared to 5% of subjects receiving placebo, and anaphylaxis was reported in 5% of subjects receiving pegloticase and 0% of subjects receiving placebo (Pegloticase (KRYSTEXXA) Investigator's Brochure). These adverse events are thought to be related to the development of anti-drug antibodies and can be reduced by avoiding infusions in patients who initially respond and then have a rebound of their serum uric acid above 6 mg/mL. These anti-drug antibodies are also associated with loss of efficacy as reflected in this increase in sUA levels [Schellekens 2005; Sundy et al, 2011].

Reducing anti-pegloticase antibodies via pre-treatment with, and concomitant administration of an immune-modifying drug, methotrexate (MTX), has been shown to be useful in other infused products, such as adalimumab, in the setting of rheumatoid arthritis treatment [Burmester GR, Kivitz AJ, Kupper H, 2015]. This study will test whether the loss of response to pegloticase can be prevented or delayed by the pre-treatment and concomitant use of MTX with pegloticase.

7.1.2 Pegloticase

Pegloticase is efficacious in reducing sUA levels and improving clinical signs and symptoms of gout. The risks of pegloticase use are detailed in the full prescribing information and include:

- 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 should begin a regimen of colchicine (0.6 mg/day) and/or nonsteroidal anti-inflammatory drug (NSAID) and/or low-dose prednisone (≤10 mg/day) prophylaxis ≥1 week before the first dose of pegloticase and 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. All subjects who experience a gout flare during the study will be prescribed anti-inflammatory treatment (e.g., NSAIDs, colchicine), as deemed clinically indicated by the study physician.

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 (60 mg or 180 mg orally based on the Principal Investigator's discretion) the day before each infusion; fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) and acetaminophen (1000 mg orally) the morning of each infusion; and methylprednisolone (125 mg IV) given over the infusion duration 10-30 minutes (recommended) or hydrocortisone (200 mg IV) will be administered immediately prior to each infusion.

The risk of anaphylaxis and IRs is higher in patients whose sUA level increases to >6 mg/dL. Therefore, beginning with Week 2, 2 pre-dose blood samples (within 48 hours prior to dosing pegloticase) will be obtained to verify the sUA level is ≤6 mg/dL prior to infusion of pegloticase (see Section 9.5.1.1). A subject with sUA level >6 mg/dL at 2 consecutive study visits, beginning with the Week 2 Visit, will be classified as a non-responder and complete the End of Pegloticase Treatment Visit within 2 weeks of the subjects last infusion. The subject will return for study visits (without treatment). See Section 9.3.3.1.1 for details.

Before starting pegloticase, subjects should discontinue oral urate-lowering therapy and not institute therapy with these agents while taking pegloticase.

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

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:	$C_xH_yN_{1632}O_zS_{32}$ Wherein, x = ~22,920, y = ~43,095, z = ~10,191
Molecular weight:	Monomer pegloticase approximately 545 kDa *(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:	$\{[H_3C-O-(CH_2CH_2-O)_m-CO-]_n-NH-$ **[TYKKNDEVEF VRTGYGKDMI KVLHIQRDGK YHSIKEVATT VQLTLSSKKD YLHGDNSDVI PTDTIKNTVN VLAKFKGIKS IETFAVTICE HFLSSFKHVI RAQVYVEEVP WKRFEKNGVK HVHAFIYTPT GTHFCEVEQI RNGPPVIHSG IKDLKVLKTT QSGFEGFIKD QFTTLPEVKD RCFATQVYCK WRYHQGRDVD FEATWDTVRS IVLQKFAGPY DKGEYSPSVQ KTLYDIQVLT LGQVPEIEDM EISLPNIHYL NIDMSKMGLI NKEEVLLPLD NPYGKITGTV KRKLSSRL]**$\}_4$ Wherein, m=~225, n=~10.2 and each uricase monomeric subunit having the amino acid sequence listed above. 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 pegloticase (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 pegloticase (KRYSTEXXA) Investigator's Brochure for detailed information.

7.1.2.4 Clinical Experience

7.1.2.4.1 Introduction

Pegloticase was granted orphan designation by the FDA on 21 February 2001 [redacted] 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.

7.1.2.4.2 Efficacy

Results of the 2 pivotal Phase 3 studies demonstrated that pegloticase 8 mg infused every 2 weeks results in clinical improvements and disease modification and provides an effective therapy for the control of the clinical consequences of hyperuricemia in patients with symptomatic gout in whom conventional therapy is contraindicated or has been ineffective, with a favorable risk/benefit profile. The principal safety risks associated with pegloticase include anaphylaxis, IRs, and gout flares. The longer-term exposure evidenced by the open-label extension study supports the benefit-to-risk assessment of 8 mg of pegloticase IV every 2 weeks as an effective therapy in chronic gout patients, particularly those with tophi who are unresponsive to other therapies.

7.1.2.4.3 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 [redacted] 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.

7.1.2.4.4 Safety

The principal safety risks associated with pegloticase include anaphylaxis, IRs, and gout flares. Pegloticase has not been formally studied in patients with congestive heart failure, but some subjects in the clinical trials experienced exacerbation. Exercise caution when using pegloticase in patients who have congestive heart failure and monitor patients closely following infusion.

The data support that monitoring of sUA and discontinuation of pegloticase therapy in patients who lose the ability to maintain uric acid <6 mg/dL can lead to the avoidance of the majority of IRs and unnecessary exposure to drug. The longer-term exposure evidenced by the open-label extension study supports the benefit-to-risk assessment of 8 mg of pegloticase IV every 2 weeks as an effective therapy in chronic gout patients, particularly those with tophi who are unresponsive to other therapies.

Based on the results observed in the Phase 4 observational study of pegloticase 8 mg IV every 2 weeks for up to 52 weeks, pegloticase remains a beneficial treatment for adult patients with chronic gout refractory to conventional therapy. The safety profile remains unchanged for pegloticase in terms of IRs, anaphylaxis, and other SAEs. Limiting future infusions once sUA has been demonstrated to be elevated on 2 consecutive occasions appeared to decrease the risk of anaphylaxis, which improves the benefit-to-risk equation favoring the use of pegloticase. No new safety information was identified.

7.1.3 Methotrexate

MTX is a folic acid reductase inhibitor used as a disease-modifying, anti-rheumatic drug for the treatment of autoimmune diseases.

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. 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. 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. In the Phase 3 program, 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 immunomodulating therapy. Various methods are used to reduce antibody production, the most common of which is the use of traditional rheumatoid arthritis disease-modifying drugs, such as MTX, azathioprine, mycophenolate mofetil, leflunomide, 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 reduce antidrug antibodies against pegloticase that lead to loss of response and that are associated with IRs, thereby allowing patients to receive a longer course of therapy or repeated courses of therapy, as needed.

7.3 Rationale for Dose Selection

The dose and dose regimens used in this study are those specified by the prescribing information for pegloticase and MTX, respectively.

8 STUDY OBJECTIVES

The overall objective of the study is to assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of the concomitant use of MTX with pegloticase to enhance the response rate seen with pegloticase alone in adults with uncontrolled gout.

Primary Objective

The primary objective is to estimate the response rate during Month 6 (Weeks 20, 22, 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 in subjects receiving pegloticase with MTX.

Secondary Objectives

- Estimate 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 in subjects receiving pegloticase with MTX.
- Estimate 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, 22 and 24) combined in subjects receiving pegloticase with MTX.
- Estimate the 5 mg/dL response rate during Month 3, during Month 6, and Overall (Months 3 and 6 combined), as measured by the sustained normalization of sUA to <5 mg/dL for at least 80% of the time in subjects receiving pegloticase with MTX.

- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in sUA in subjects receiving pegloticase with MTX.

Exploratory Objectives

- Estimate 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 in subjects receiving pegloticase with MTX.
- Estimate 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 in subjects receiving pegloticase with MTX.
- Estimate the 5 mg/dL response rate during Month 9 (Weeks 32, 34 and 36), as measured by the sustained normalization of sUA to <5 mg/dL for at least 80% of the time during Month 9 in subjects receiving pegloticase with MTX.
- Estimate the 5 mg/dL response rate during Month 12 (Weeks 48, 50 and 52), as measured by the sustained normalization of sUA to <5 mg/dL for at least 80% of the time during Month 12 in subjects receiving pegloticase with MTX.
- Estimate the time to first sUA >6 mg/dL in subjects receiving pegloticase with MTX.
- Estimate the time to two consecutive sUAs >6 mg/dL (stopping rule) in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Week 24, 36 and 52 in urate volume and gout erosions using DECT scan of the hands and feet in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline in number of joints affected by tophi in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in tender joint count (68 point scale) in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in swollen joint count (66 point scale) in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in the Health Assessment Questionnaire – Disability Index (HAQ-DI) in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in the HAQ pain score in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in the HAQ health score in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in patient global assessment of gout in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in physician global assessment of gout in subjects receiving pegloticase with MTX.

- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in subject assessment of average, least, and worst joint pain in subjects receiving pegloticase with MTX.
- Estimate the proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36, and 52 in subjects receiving pegloticase with MTX.
- Assess the PK of pegloticase in subjects receiving concomitant MTX.
- Assess the incidence of anti-PEG and anti-Uricase IgG antibodies.

Safety and Tolerability Objectives

- Assess the incidence of infusion reactions (IRs), anaphylaxis, gout flares, cardiovascular events, and the adverse event (AE/SAE) profile overall and potentially attributed to the combination of pegloticase and MTX.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a multicenter, open-label, efficacy and safety study of pegloticase in combination with MTX in adult subjects with uncontrolled gout.

The study design will include: 1) up to a 2-week Screening Period (screening should be complete within 2 weeks prior to Week -4), 2) a 4-week MTX Run-in Period (Week – 4 through Day 1); 3) a 52-week Pegloticase + IMM (Pegloticase + MTX) Period 4) a Safety Follow-up (Phone/Email/Site Visit) and 5) a 3 and 6 month Post Treatment Follow-up.

All subjects who meet eligibility criteria at Screening will begin oral MTX at a dose of 15 mg weekly for 4 weeks prior to the first dose of pegloticase.

Subjects will also take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) and continuing until prior to the Week 52 Visit. Subjects must be able to tolerate MTX at a dose of 15 mg during the MTX Run-in (Week -4 through Day 1) to be eligible to participate in the Pegloticase + IMM Period. Subjects who are unable to tolerate MTX at a dose of 15 mg during the MTX Run-in Period will be considered screen failures.

Subjects who take at least one dose of MTX and who are females of childbearing potential, will receive a safety follow-up Phone Call/E-mail/Site Visit approximately 30 days after the last dose of MTX to verify at least one ovulatory cycle has occurred after the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. Subjects who receive at least one dose of MTX and who are non-vasectomized males, will be asked, 3 months after MTX discontinuation, regarding partner pregnancy.

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 (60 mg or 180 mg orally based on the Principal Investigator's discretion) will be taken the day before each infusion; fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) given over the infusion duration 10-30 minutes (recommended) or hydrocortisone (200 mg IV) will be administered 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 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 must be taken ≥60 minutes prior to each pegloticase infusion.

After Day 1, if a subject becomes unable to tolerate 15 mg of MTX, the MTX dose may be reduced and/or discontinued, and the subject may remain in the study (see Section 9.4.6.3.2.2).

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

Serum samples for measurement of sUA levels will be collected at the Screening Visit, the Week -4 Visit (prior to the first dose of MTX), and the Week -2 Visit during the MTX 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; at the non-infusion Week 52/End of Study/Early Termination Visits and at the Post Treatment 3 and 6 Month Follow-up Visits. Additional serum samples for sUA levels will be collected at optional non-

infusion (Frequent Sampling) Visits at Weeks 1 and 7. If applicable an sUA sample will need to be collected at the End of Pegloticase Visit if a subject does not continue treatment. Subjects with sUA level >6 mg/dL at 2 consecutive visits beginning at 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).

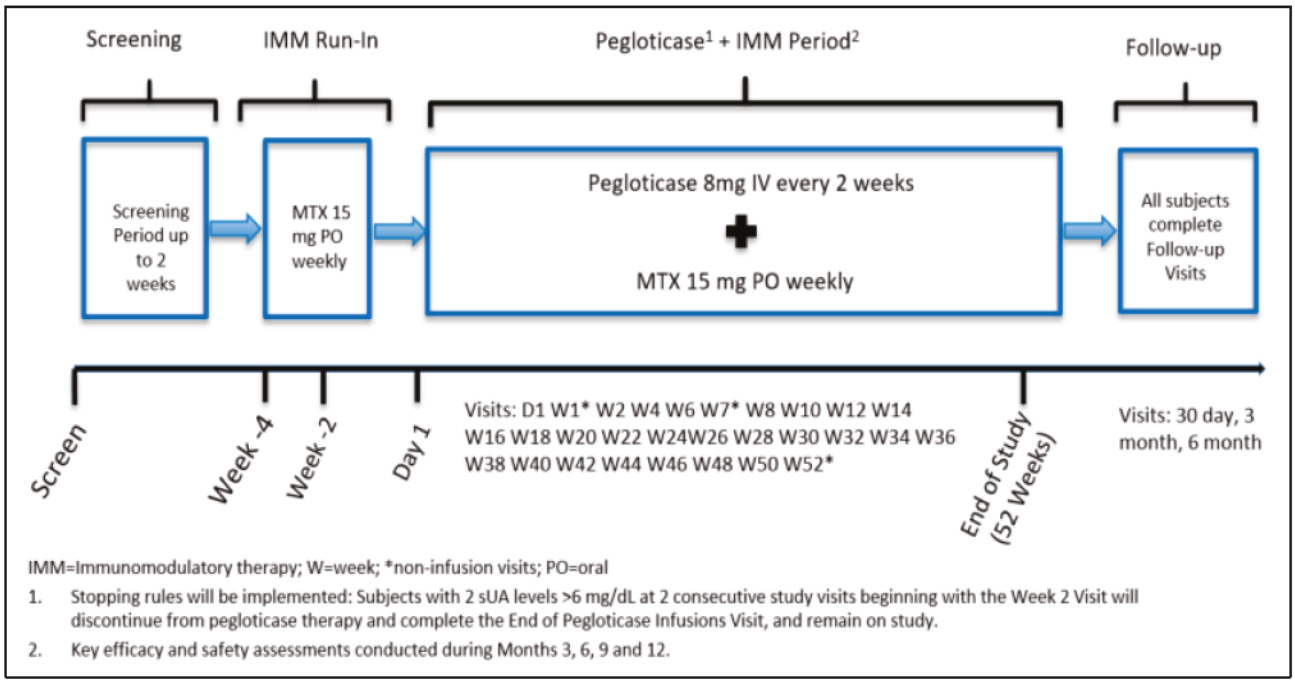
Samples for measurement of sUA levels, PK analysis of pegloticase, pegloticase immunogenicity and MTX Polyglutamate analysis will be collected at visits indicated in the Schedule of Assessments (Section 2.1).

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.

The total blood volume to be collected from each subject during this study is approximately 700 mL, increased to 750 mL for the subjects participating in the optional visits at Week 1 and Week 7.

An overview of the study design is presented in the schematic below, and details of study activities are provided in Section 9.1.

Figure 9.1 Schematic of Study Design



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.

9.2 Discussion of Study Design

This study is a multicenter, open-label, efficacy and safety study of pegloticase in combination with 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 immunomodulating 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].

The study design will include: 1) up to a 2-week Screening Period (screening should be complete within 2 weeks prior to Week -4), 2) a 4-week MTX Run-in Period; 3) an End of Pegloticase Treatment Visit if applicable 4) a 52-week Pegloticase + IMM (Pegloticase + MTX) Period 5) a Safety Follow-up (Phone/Email/Site Visit) and 6) a 3 and 6 month Post Treatment Follow-up.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Eligible subjects must meet 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 to ≤65 years of age.
4. 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 the Screening/MTX Run-in Period; 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 -4 (start of MTX dosing) and continue for 30 days after the last dose of pegloticase or at least one ovulatory cycle after the last dose of MTX (whichever is the longest duration after the last dose of pegloticase or 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.
5. Men who are not vasectomized must not impregnate their female partner during the study and for at least 3 months after the last dose of MTX.
6. Hyperuricemia at the Screening, Week -4, or Week -2 Visit of the Screening/MTX Run-in Period, as documented by sUA ≥6 mg/dL.
7. Uncontrolled gout, defined as meeting the following criteria:
   - sUA ≥6 mg/dL prior to entry into the Pegloticase + IMM Period (any laboratory tests during screening up to and including during the MTX Run-in Period) and at least 1 of the following:
     - inability to maintain sUA <6 mg/dL on other urate-lowering therapy
     - intolerable side effects associated with current urate-lowering therapy
     - functionally limiting tophaceous deposits (including those detected clinically or by DECT imaging)
8. Able to tolerate MTX 15 mg for 4 weeks during the Screening/MTX Run-in Period prior to the first dose of pegloticase.

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).
2. Any serious acute bacterial infection, unless treated and completely resolved with antibiotics at least 2 weeks prior to the Week -4 Visit of the Screening/MTX Run-in Period.
3. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis.

4. Current immunocompromised condition, including current or chronic treatment with systemic immunosuppressive agents, including prednisone >10 mg/day or equivalent dose of other corticosteroid.
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 (tested at Screening Visit).
9. Glucose -6-phosphage dehydrogenase (G6PD) deficiency (tested at the Screening Visit).
10. Severe chronic renal impairment (glomerular filtration rate <25 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) at the end of the Screening/MTX Run-in Period.
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 (KRYSTEXXA), 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 -4 or plans to take an investigational drug during the study.
18. Current liver disease, as determined by alanine transaminase or aspartate transaminase levels >3 times upper limit of normal at the Screening Visit.
19. Currently receiving systemic or radiologic treatment for ongoing cancer, excluding non-melanoma skin cancer.
20. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix.
21. Uncontrolled hyperglycemia with a plasma glucose value >240 mg/dL at screening that is not subsequently controlled by the end of the Screening/MTX Run-in Period.
22. Diagnosis of osteomyelitis.

23. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
24. 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.
25. Alcohol use in excess of 3 alcoholic beverages per week.
26. Currently receiving allopurinol and unable to discontinue medication 7 days prior to MTX dosing at Week -4 and unable to discontinue treatment during the duration of the study.

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, 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 10, 12, 14, 20, 22, 24, 32, 34, 36, 48, 50 and 52, so that sUA labs and other key assessments can be completed. Subjects who have stopped infusions, may complete the other 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 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:

Each subject will be followed up for at least 6 months 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 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 will be considered screen failures. In addition, subjects who are unable to tolerate MTX at an oral dose of 15 mg weekly during the MTX Run-in Period will be considered screen failures. Screen failure subjects who are females of childbearing potential who took at least one dose of MTX, will receive a Safety Follow-up Phone call/E-mail/Site Visit approximately 30 days after the last dose of MTX to verify at least one ovulatory cycle after the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed at the study site. Screen failure subjects who receive at least 1 dose of MTX and are non-vasectomized males will receive a Phone/E-mail/Site Visit 3 months after MTX discontinuation regarding partner pregnancy.

Screen failure subjects 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 the subject can satisfy all of the eligibility criteria.

9.4 Treatments

9.4.1 Treatments Administered

During the MTX Run-in Period, which begins 4 weeks prior to the first dose of pegloticase, subjects will take oral MTX at a dose of 15 mg weekly. Subjects will be instructed to take MTX weekly on the same day each week (if dosing more frequently than once in a day (i.e. BID, TID), the total MTX dose should be taken within 24 hours, preferably the same calendar day) and record the date and time of dose/s in the dosing calendar. During the Pegloticase + IMM Period, MTX should be taken 1 to 3 days prior to pegloticase infusion; however, if a subject does not do so, MTX must be taken ≥60 minutes prior to pegloticase infusion. During the MTX 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, MTX should be taken 1 to 3 days prior to pegloticase infusion; however, if a subject does not do so, MTX must be taken ≥60 minutes prior to pegloticase infusion. If a subject becomes unable to

tolerate the prescribed dosage of MTX during the Pegloticase + IMM Period, the dosage may be decreased (see Section 9.4.6.3.2.2).

During the pegloticase +IMM Period all subjects will receive pegloticase at the same dose of 8 mg administered IV every 2 weeks for a total of 26 infusions from Day 1 through Week 50, inclusive (Pegloticase + IMM Period). The date and start and stop time of infusion including the flush 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, unless medically contraindicated or not tolerated, beginning ≥1 week before the first dose of pegloticase. Standardized IR prophylaxis consisting of pre-treatment with antihistamines, acetaminophen, and corticosteroids will accompany each infusion.

9.4.1.1 Folic Acid

Subjects will take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the Week 52/End of Study/Early Termination Visit.

If the subject discontinues pegloticase due to the stopping rules or other reason, MTX and folic acid should also be discontinued.

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 (60 mg or 180 mg orally based on the Principal Investigator's discretion) the day before each infusion; fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) and acetaminophen (1000 mg orally) the morning of each infusion; and methylprednisolone (125 mg IV) given over the infusion duration 10-30 minutes (recommended) or hydrocortisone (200 mg IV) will be administered 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. Prescriptions are to be filled at a local pharmacy, as needed. The methylprednisolone or hydrocortisone 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

MTX 2.5 mg tablets for oral administration will be provided to subjects as a commercially available generic (MTX Full Prescribing Information).

A dosing calendar will be provided to subjects at the Week -4 Visit to record each dose of MTX and the date and time of each dose on each calendar day of MTX administration. Additional calendar pages may be provided on future visits as needed.

9.4.3 Labeling

Pegloticase (KRYSTEXXA) is commercially available in the United States and will be supplied by [redacted] packaged in sterile, single-use [redacted] 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 will be provided to sites by [redacted] 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 after the Week -4 Visit for weekly dosing after visit procedures and inclusion/exclusion criteria 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 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 subject drug logs/electronic logs to account for MTX dispensed, and subject compliance will be monitored by the site at each visit (see Section 9.4.9).

Subjects will bring the MTX dosing calendar to each study visit for assessment of compliance. Subjects will bring the MTX bottle to each visit for a compliance check by the site. The site will manually count the pills 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 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

[redacted] will supply study drugs (pegloticase and MTX) to clinical sites. Ancillary supplies for dosing will be provided by the study site (i.e., infusion bags containing normal 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 Run-in Period, which begins 4 weeks prior to the first dose of pegloticase, subjects will take oral MTX at a dose of 15 mg weekly. Subjects will be instructed to take MTX once weekly on the same day each week (if dosing more frequently than once in the day (i.e. BID, TID), the total MTX dose should be taken within the same calendar day) and record the date and time of each dose on each calendar day of MTX administration.

During the MTX 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. If a dose is missed, or if infusion schedules are adjusted and MTX dose must be moved from the regular day, it is recommended that the doses are at least 5 days apart if possible, however it is safe for MTX doses to be administered with a minimum of 3 days apart.

During the Pegloticase + IMM Period, subjects will be instructed to take MTX 1 to 3 days prior to the dose of pegloticase; however, if a subject does not do so, MTX must be taken ≥60 minutes prior to pegloticase infusion. Subjects will dose Methotrexate weekly until one week after the last infusion.

If a subject becomes unable to tolerate the prescribed dosage of MTX after Day 1 during the Pegloticase + IMM Period, the dosage may be decreased (see Section 9.4.6.3.2.2).

Refer to Section 9.4.11 for contraception requirements.

Subjects will take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the Week 52 Visit or the last infusion visit. Folic acid will be supplied by a local pharmacy.

Pegloticase

All subjects will receive pegloticase at the same dose of 8 mg administered IV every 2 weeks for a total of 26 infusions from Day 1 through Week 50, inclusive (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

Administration 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 Dose Titration Algorithm and Intolerance Criteria

During the MTX Run-in a subject 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, subject will not be considered a screen failure on the basis of that symptom.

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

Lab Parameters	Value	MTX Dose Change
WBC	3.0 x 10^9/L ~ 3.5 x 10^9/L	Decrease to 10 mg
	< 3.0 x 10^9/L	Temporary stop
Platelets	< 50 x 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 (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 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 dose by 2.5 mg and reassess in 2 weeks.
2. If liver enzymes remain ≤1.5 × upper limit of normal, increase MTX or dose by 2.5 mg and reassess in 2 weeks.

Improvement of other laboratory abnormalities potentially attributed to MTX or 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 prednisone (e.g. 20 mg) 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

This study is an open-label, single-arm design in which all subjects will receive the same study drugs (i.e., MTX and pegloticase).

9.4.8 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 and up 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.

9.4.9 Restricted Medications

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

- Oral urate-lowering therapies including allopurinol, febuxostat, probenecid, lesinurad, or other ULT for gout.
- Any PEG-conjugated drug
- Any other investigational agent
- Methotrexate (other than study 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.
- Systemic immunosuppressive agents

9.4.10 Treatment Compliance

A dosing calendar will be provided to subjects at the Week -4 Visit for recording each dose of MTX on each calendar day of MTX administration (Additional calendar pages may be provided

at future visits as required). The dosing calendar and bottle of MTX should be brought to each study visit for assessment of compliance with MTX. Adherence to the MTX regimen will also be recorded by the study coordinator at study visits in the eCRF by recording the date of each 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 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.

9.4.11 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 -4 (start of MTX dosing) and continue for 30 days after the last dose of pegloticase or at least one ovulatory cycle after the last dose of MTX (whichever is the longest duration after the last dose of pegloticase or 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 a female partner of reproductive potential during the study and for at least 3 months after the last dose of MTX. 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 from blood samples, tender and swollen joint counts, patient and physician global assessment of gout, joint pain, urate volume and gout erosion due to gout by DECT.

9.5.1.1 Serum Uric Acid

Serum samples for measurement of sUA levels will be collected at the Screening Visit (within 2 weeks prior to the first dose of MTX at Week -4), the Week -4 Visit (prior to the first dose of MTX), and the Week -2 Visit during the MTX Run-in Period; within 48 hours prior to each pegloticase infusion (except on Day 1 when only 1 pre-infusion sample is required) and after the end of each pegloticase infusion prior to discharge, from the Pegloticase + IMM Period through

week 24 and at Weeks 32, 34, 36, 48 and 50; within 48 hours prior to each pegloticase infusion at Weeks 26, 28, 30, 38, 40, 42, 44 and 46 during the Pegloticase + IMM Period; and at the at the End of Pegloticase Infusions Visit (if applicable); at the Week 52/End of study/Early Termination Visit and Month 3 and Month 6 Visits. (Section 2.1) Optional (subjects who agree to participate) visits for frequent sampling for additional non-infusion visit sUA sampling (random, morning preferred) will occur at Week 1 and Week 7.

Two separate samples/tubes of blood will be collected within 48 hours prior to the pegloticase infusion for assessment of sUA (except on Day1 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. Each sample/tube will be labelled with the date and time of the sample collection. The date and time of blood sample collection will be recorded. See the Laboratory Manual for instructions for alternate scenarios.

A subject with 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 and remain on study.

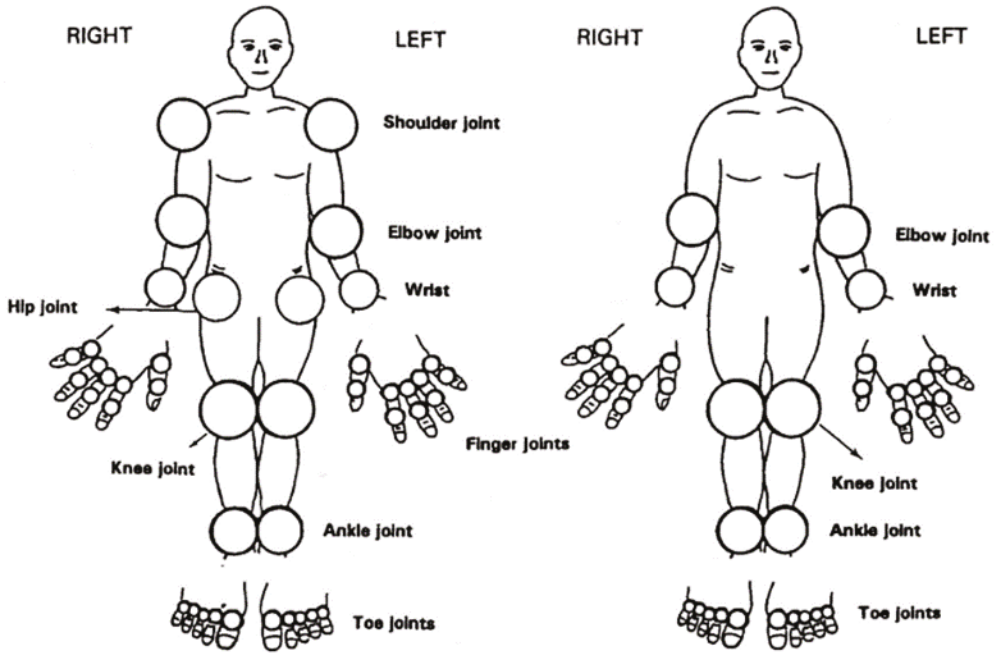
Samples that result in discordant results between local and central laboratories will be evaluated and discussed with the Investigator and the Sponsor's Medical Monitor on a case-by-case basis to determine whether the subject should continue on study or discontinue.

9.5.1.2 Tender and Swollen Joint Counts

Tender and swollen (excludes hip) joint counts will be recorded at the Week -4 (prior to the first dose of MTX) Visit during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks14, 24 and 36 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 and the Post Treatment 3 and 6 month Follow-up visits (Section 2.1).

Tender and swollen joint counts will be assessed by physical examination and documented using the rheumatoid arthritis 66-68 method shown in Figure 9.2Rheumatoid Arthritis 66-68 Tender and Swollen Joint Counts or via 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 Patient Global Assessment

The patient global assessment will be collected at the Screening and Week -4 (prior to the first dose of MTX) Visits during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if applicable); the Week 52/End of Study/Early Termination Visit and the Post Treatment Periods 3 and 6 Month Follow-up Visits (Section 2.1). Subjects will respond to the statement, "Considering all the ways that gout affects you, circle the number below that best represents how your gout has affected you over the last week" using a numeric rating scale ranging from 0 (excellent) to 10 (very poor) (see Appendix 17.3).

9.5.1.4 Physician Global Assessment

The physician global assessment will be collected at the Screening and Week -4 (prior to the first dose of MTX) Visits during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if applicable), the Week 52/End of Study/Early Termination Visit and the Post Treatment Periods 3 and 6 Month Follow-up Visits (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 17.4).

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

9.5.1.5 Joint Pain Assessment

Joint pain will be assessed at the Screening and Week -4 (prior to the first dose of MTX) Visits during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if applicable); the Week 52/End of Study/Early Termination Visit and the Post Treatment Periods 3 and 6 Month Follow-up Visits (Section 2.1). Subjects will respond to the following statements using a numeric rating scale ranging from 0 (no joint pain) to 10 (worst possible joint pain) (see Appendix 17.5).

- Rate the average pain you have had in your joints during the last week.
- Rate the least pain you have had in your joints during the last week.
- Rate the worst pain you have had in your joints during the last week.

9.5.1.6 Dual-energy Computed Tomography (DECT)

For sites with DECT capability, DECT will be obtained at Day 1 and Weeks 24, 36 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if applicable), the Week 52/End of Study/Early Termination Visit during the and 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.

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

9.5.2 Quality-of-Life Assessment

The HAQ will be administered at the Screening and Week -4 (prior to the first dose of MTX) Visits during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if applicable), the Week 52/End of Study/Early Termination Visit and the Post Treatment Periods 3 and 6 Month 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 (Appendix 17.2). 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 asks subjects to record how much pain they have had in the past week on a scale of 0 to 100, where zero represents "no pain" and 100 represents "severe pain".

The HAQ health scale is a measure of overall health. Subjects are asked to rate how well they are doing on a score of 0 to 100, where zero represents "very well" and 100 represents "very poor" health.

9.5.3 Pharmacokinetic and Anti-drug Antibody Measurements

Serum samples for PK analysis of pegloticase will be collected prior to the pegloticase infusion and after the end of infusion (prior to discharge) on Day 1 and at the Weeks 2, 4, 6, 8 and 36 Visits and prior to the pegloticase infusion only at the Weeks 10, 14, 18, 22, 24; at the End of Pegloticase Infusions Visit (if applicable); and the Week 52/End of Study/Early Termination Visits. Visits for frequent sampling of a subset of subjects who consent for additional non-infusion visit PK sampling will occur at Weeks 1 and 7.

Immunogenicity of pegloticase will be assessed via serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies. Samples will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 2, 4, 6, 8, 10, 14, 18, 22, 24, 36, at the End of Pegloticase Infusions Visit (if applicable); and 52/End of Study/Early Termination Visits and Post Treatment 3 month Follow-up Visit. Visits for frequent sampling of a subset of subjects who consent for additional non-infusion visit PK sampling will occur at Weeks 1 and 7. 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.

Blood samples will be collected prior to pegloticase infusion on Day 1 and at the Weeks 4, 8, 22 and 36 Visits during the Pegloticase + IMM 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.

9.5.4 Safety Variables

Safety will be assessed via AE and concomitant medication use monitoring, physical examinations, vital signs, clinical safety laboratory evaluations (hematology, chemistry, urine uric acid: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:

a. Results in death

b. 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.
c. 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.
d. 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.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via a medicinal product
g. 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 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.

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 1 hour post infusion. Other AEs that occur outside of the 1-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.

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]:

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

- The following cardiovascular events will be collected. Major Adverse Cardiovascular Events (MACE) defined as:
    - Non-Fatal Myocardial Infarction: The presence of at least 2 of the 3 following criteria: 1) chest pain consistent with angina, 2) abnormal values of cardiac enzymes (> upper limit of normal of the MB fraction of creatinine phosphokinase and/or troponin that follows a pattern of myocardial injury), 3) myocardial injury current (ST segment elevation) or the development of new Q waves in 2 contiguous leads of the electrocardiogram.
    - Non-Fatal Stroke: ischemic or hemorrhagic stroke defined as an acute, focal neurologic event that persisted for > 24 hours. If neurologic symptoms last for < 24 hours but magnetic resonance imaging (MRI) confirms an infarct, it will be considered as a stroke. Confirmation by imaging studies (magnetic resonance imaging or computerized tomography of the brain) will be sought in all cases, but will not be an absolute requirement for consideration of the event.
    - Cardiovascular deaths: including any death from a cardiovascular cause including: myocardial infarction, stroke, heart failure, arrhythmic death, aortic dissection or rupture, any fatal thromboembolic event, sudden cardiac death, any death of unknown cause and unwitnessed death.
- Congestive heart failure defined as: hospitalization or prolonged (> 12 hours)

emergency department visit due to dyspnea, shortness of breath, with progressive edema accompanied by clinical findings of pulmonary vascular congestion. Radiographic and/or echocardiographic documentation is desirable but not required. Treatment by intravenous (Parenteral) diuretics or inotropes is required to confirm this diagnosis versus ultrafiltration, hemodialysis or left ventricular assist devices.

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.

AEs recorded before the first dose of MTX in the Run-In Period will be recorded as medical history.

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)
- Grade 3 (severe) – prolonged symptoms, reversible, major functional impairment, prescription medications/partial relief, hospitalized <24 hours, temporary or permanent study drug discontinuation
- 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 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 [redacted]
E-mail [redacted]

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 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 [redacted] 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 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. [redacted] 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 [redacted].

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

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 participation in the study and/or the follow-up period 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 at the end of participation in the study and/or the follow up period. 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.

Male subjects who are not vasectomized must not impregnate their female partner during the study until at least 3 months after the last dose of MTX.

Information must be obtained and reported if a female subject suspects that she has become pregnant during the study (including the MTX Run-in Period) up to 30 days after the last dose of study treatment (either pegloticase or MTX), or if a female partner of male subject suspects that she has become pregnant during the study (including the MTX Run-in Period) up to 3 months (approximately 90 days) after their male subject partner discontinues 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 and Week -4 Visits.

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 -4 and at all infusion visits during the Pegloticase + IMM Period 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. (Section 2.1). 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.

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; 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, and neurological status. The exam will include assessment for presence of tophi, as well as gout history and symptom severity (Section 2.1).

A targeted physical examination per the investigator judgement but at a minimum should include heart, lungs and abdominal exam and include a joint and skin evaluation and assessment of AEs at Week -4, Day 1, and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20, 24, 36,

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.

Physical examination findings at screening should be recorded on the medical and surgical history eCRF.

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 on Day 1 before the pegloticase infusion for all subjects and at the discretion of the Investigator thereafter (Section 2.1).

9.5.4.7 Clinical Laboratory Safety Tests

Blood (for hematology and clinical chemistry) and urine (for uric acid:creatinine ratio) samples will be collected at the Screening, Week -4 (prior to the first dose of MTX), and Week -2 Visits during the Screening/MTX Run-in Period; prior to pegloticase infusion on Day 1 and at the Weeks 2, 6, 14, 22, 24 and 36, Visits during the Pegloticase + IMM Period; 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.

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 abbreviated MDRD equation : creatinine (including calculation for eGFR calculated by the MDRD study equation : 175 x $(S_{cr[mg/dL]})^{-1.154}$ x $(age)^{-0.203}$x (0.742 if female) x (1.212 if African American) or 175 x $(S_{cr[\mu mol/L]}/88.4)^{-1.154}$ x $(age)^{-0.203}$x (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: uric acid:creatinine ratio and human chorionic gonadotropin (at all visits except the Screening Visit 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 by asking subjects the following questions at the time points specified in Section 2.1. To be considered a gout flare, subjects must answer positively to 3 of the following 4 questions [Gaffo et al, 2012].

1. Have you had a gout flare in your joints in the last 2 weeks (Screening Visit only) or since last visit (all other visits)? (Yes/No)
2. If yes to flare, was there pain in the joint(s) that was different than normal? (Yes/No)
3. If yes to flare, was there pain in the joint(s) at rest that was greater than a 3 out of 10 (where 0 = no pain and 10 = the worst pain imaginable)? (Yes/No)
4. If yes, was there swelling in the joint(s)? (Yes/No)

Additionally, the subject should report:

- the joints affected using a subject-facing diagram (see Appendix 17.6);
- the therapy taken to treat the gout flare (part of standard AE assessment);
- how long the gout flare lasted and when it resolved (part of standard AE assessment).

Each confirmed flare will be captured in the eCRF to allow summary of the number of flares. Intensity of gout flares will be documented. Gout Flares should be captured as an Adverse Events/Serious Adverse Event (see 9.5.4.1)

9.5.5 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).

9.5.6 Study Procedures

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

9.5.6.1 Screening/MTX Run-in Period

During the Screening /MTX Run-in Period, study candidates will be evaluated for study entry according to the stated inclusion and exclusion criteria (Section 2.1). The following procedures will be performed during screening to establish each candidate's eligibility for enrollment into the study.

9.5.6.1.1 Screening Visit (Within 2 Weeks Prior to the First Dose of MTX at Week -4)

- 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).

- 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. History of non-gout medication use in the year prior will be collected (see Section 9.4.9 for restrictions regarding medications).

- Assess for the presence of tophi.
- Obtain demographic information.
- Perform a complete physical examination.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate), including measurements of height and weight (see Section 9.5.4.4).
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a urine sample for uric acid:creatinine ratio.
- 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), G6PD, and HIV antibody.
- Administer HAQ and record patient and physician global assessments and joint pain assessment responses.
- Inquire about AEs.

9.5.6.1.2 Week -4

- Confirm study eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Collect medical/surgical history, substance use history, and medication history (see Section 9.4.9 for restrictions regarding medications).
- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.
- 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 for uric acid:creatinine ratio.
- 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).
- Collect swollen/tender joint counts; administer HAQ; and record patient and physician global assessments and joint pain assessment responses.
- Provide dosing calendar for subjects to record the date and time they take 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.
- Screen failure subjects that take MTX during Week -4 or Week -3, and who are females of childbearing potential, will receive a safety follow-up phone call/e-mail/site visit 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. Screen failure subjects who are non-vasectomized males, a phone/e-mail/site visit inquiry will be conducted 3 months after MTX discontinuation regarding partner pregnancy.

9.5.6.1.3 Week -2

- Confirm study eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a urine sample for uric acid:creatinine ratio.
- 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 and re-dispense MTX.

- Document gout flares and intensity.
- Ask Yes/No question regarding folic acid and gout flare prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Collect substance use history, and medication history (see Section 9.4.9 for restrictions regarding medications).
- Inquire about AEs.
- Screen failure subjects that taken MTX during Week -4 or Week -3, Week -2 or Week -1, and who are females of childbearing potential, will receive a safety follow-up phone call/e-mail/site visit 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. Screen failure subjects who are non-vasectomized males, a phone/e-mail/site visit inquiry will be conducted 3 months after MTX discontinuation regarding partner pregnancy.

9.5.6.2 Pegloticase + IMM Period

9.5.6.2.1 Day 1

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

- Obtain 1 blood sample for measurement of sUA prior to the pegloticase infusion.
- Confirm study eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Administer MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX within the previous 1 to 3 days.
- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.
- Document gout flares and intensity.
- Record vital signs (blood pressure [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]), including measurement of weight prior to infusion (see Section 9.5.4.4).
- Perform 12-lead ECG prior to the pegloticase infusion.

- Collect swollen/tender joint counts; administer HAQ; and record patient and physician global assessments and joint pain assessment responses.
- Assess MTX compliance and re-dispense 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 for uric acid:creatinine ratio.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- 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 blood samples for pegloticase PK analysis prior to the infusion.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone or hydrocortisone) (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 a blood sample (1 sample) for measurement of sUA after the end of the pegloticase infusion prior to discharge.
- Obtain blood samples for pegloticase PK analysis after the end of the infusion prior to discharge.
- Inquire about AEs and concomitant medication use.
- Perform DECT (if applicable).

9.5.6.2.2 Week 1 (Non-infusion visit for those who consent only)

- Inquire about AEs and concomitant medication use.
- Obtain blood samples for pegloticase PK analysis.

- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies.
- Obtain a blood sample (1 sample) for measurement of sUA.

9.5.6.2.3 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 ≥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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 for uric acid:creatinine ratio.
- 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 infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.

- Obtain blood samples for pegloticase PK analysis after the end of the infusion prior to discharge

- Inquire about AEs and concomitant medication use.

9.5.6.2.4 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 discontinue treatment and remain in the study.

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

- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.

- Document gout flares and intensity.

- Record vital signs (blood pressure [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).

- Assess MTX compliance and re-dispense MTX.

- Obtain blood samples for MTX Polyglutamate analysis prior to the infusion.

- Obtain blood samples for pegloticase PK analysis prior to the infusion.

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

- 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 or hydrocortisone) (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 blood samples for pegloticase PK analysis after the end of the infusion prior to discharge.
- Obtain a blood sample (1 sample) for measurement of sUA after the end of pegloticase infusion prior to discharge.
- Inquire about AEs and concomitant medication use.

9.5.6.2.5 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 discontinue treatment and remain in the study.
- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 uric acid:creatinine ratio.
- Obtain blood samples for pegloticase PK analysis prior to the infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.
- Obtain blood samples for pegloticase PK analysis after the end of the infusion prior to discharge.
- Inquire about AEs and concomitant medication use.

9.5.6.2.6 Week 7 (Non-infusion visit for those who consent only)

- Inquire about AEs and concomitant medication use.
- Obtain blood samples for pegloticase PK analysis
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Obtain a blood sample (1 sample) for measurement of sUA

9.5.6.2.7 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 discontinue treatment and remain in the study.

- Administer MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX within the previous 1 to 3 days.
- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.
- Document gout flares and intensity.
- Record vital signs (blood pressure [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]), including measurement of weight prior to infusion (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 MTX Polyglutamate analysis prior to the infusion.
- Obtain blood samples for pegloticase PK analysis prior to the infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- 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 or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.
- Obtain blood samples for pegloticase PK analysis after the end of the infusion prior to discharge.
- Inquire about AEs and concomitant medication use.

9.5.6.2.8 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 discontinue treatment and remain in the study.
- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 pegloticase PK analysis prior to the infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- 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 or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.
- Inquire about AEs and concomitant medication use.

9.5.6.2.9 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 discontinue treatment and remain in the study.
- Administer MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX within the previous 1 to 3 days.
- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.
- Document gout flares and intensity.
- Record vital signs (blood pressure [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.
- Inquire about AEs and concomitant medication use.

9.5.6.2.10 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 discontinue treatment and remain in the study.
- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Collect swollen/tender joint counts; administer HAQ; and record patient and physician global assessments and joint pain assessment responses.
- Assess MTX compliance and re-dispense 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 uric acid:creatinine ratio.
- Obtain a blood sample for pegloticase PK analysis prior to the infusion.
- Obtain a blood sample for MTX Polyglutamate analysis prior to the infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.

- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.

- Inquire about AEs and concomitant medication use.

9.5.6.2.11 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 discontinue treatment and remain in the study.

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

- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.

- Document gout flares and intensity.

- Record vital signs (blood pressure [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) including measurement of weight prior to infusion (see Section 9.5.4.4).

- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.
- Inquire about AEs and concomitant medication use.

9.5.6.2.12 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 discontinue treatment and remain in the study.
- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 pegloticase PK analysis prior to the infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.
- Inquire about AEs and concomitant medication use.

9.5.6.2.13 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 discontinue treatment and remain in the study.
- Administer MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX within the previous 1 to 3 days.
- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.
- Document gout flares and intensity.
- Record vital signs (blood pressure [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.

- Inquire about AEs and concomitant medication use.

9.5.6.2.14 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 discontinue treatment and remain in the study.

- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).

- Assess MTX compliance and re-dispense 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 uric acid:creatinine ratio.
- Obtain blood samples for MTX Polyglutamate analysis prior to the infusion.
- Obtain a blood sample for pegloticase PK analysis prior to the infusion.
- Obtain a blood sample for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.
- Inquire about AEs and concomitant medication use.

9.5.6.2.15 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 discontinue treatment and remain in the study.
- Administer MTX ≥60 minutes prior to pegloticase infusion if subject has not taken MTX within the previous 1 to 3 days.
- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.
- Document gout flares and intensity.

- Record vital signs (blood pressure [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]), including measurement of weight prior to infusion (see Section 9.5.4.4).
- Collect swollen/tender joint counts; administer HAQ; and record patient and physician global assessments and joint pain assessment responses.
- Assess for the presence of tophi.
- Assess MTX compliance and re-dispense 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 for uric acid:creatinine ratio.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for MTX Polyglutamate analysis prior to the infusion.
- Obtain blood samples for pegloticase PK analysis prior to the infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone or hydrocortisone) (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 a blood sample (1 sample) for measurement of sUA after the end of pegloticase infusion prior to discharge.
- Inquire about AEs and concomitant medication use.
- Perform DECT (if applicable).
- Perform Investigator assessment of Clinical Status.

9.5.6.2.16 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 discontinue treatment and remain in the study.
- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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.

9.5.6.2.17 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 discontinue treatment and remain in the study.

- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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.

9.5.6.2.18 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 discontinue treatment and remain in the study.

- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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.

9.5.6.2.19 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 discontinue treatment and remain in the study.
- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).

- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.

- Inquire about AEs and concomitant medication use.

9.5.6.2.20 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 discontinue treatment and remain in the study.

- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).

- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.
- Inquire about AEs and concomitant medication use.

9.5.6.2.21 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 discontinue treatment and remain in the study.
- Administer 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.
- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.

- Record vital signs (blood pressure [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) including measurement of weight (see Section 9.5.4.4).
- Collect swollen/tender joint counts; administer HAQ; and record patient and physician global assessments and joint pain assessment responses.
- Assess for the presence of tophi.
- Assess MTX compliance and re-dispense 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 uric acid:creatinine ratio.
- Obtain blood samples for pegloticase PK analysis prior to the infusion
- 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.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.
- Obtain blood samples for pegloticase PK analysis after the end of the infusion prior to discharge.
- Perform DECT (if applicable).
- Inquire about AEs and concomitant medication use.

9.5.6.2.22 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 discontinue treatment and remain in the study.
- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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.

9.5.6.2.23 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 discontinue treatment and remain in the study.

- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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.

9.5.6.2.24 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 discontinue treatment and remain in the study.

- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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.

9.5.6.2.25 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 discontinue treatment and remain in the study.
- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).

- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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.

9.5.6.2.26 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 discontinue treatment and remain in the study.

- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).

- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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.

9.5.6.2.27 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 discontinue treatment and remain in the study.
- Administer 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 [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and re-dispense 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 or hydrocortisone) (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 after the end of pegloticase infusion prior to discharge.
- Inquire about AEs and concomitant medication use.

9.5.6.2.28 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 discontinue treatment and remain in the study.
- Administer 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, one measurement [prior and post infusion], respiratory rate, temperature, and heart rate [prior and post infusion]) (see Section 9.5.4.4).
- Assess MTX compliance and dispense.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- 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 or hydrocortisone) (see Section 9.4.1.3**Error! Reference source not found.**).

- 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 after the end of pegloticase infusion prior to discharge.
- 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.

9.5.6.3 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 Weeks 10, 12, 14, 20, 22, 24, 32, 34, 36, 48, 50 and 52, so that sUA labs and other key assessments can be completed. Visits between these key efficacy and safety collection visits, for subjects who have stopped infusions, may be completed in person or via a telephone visit option to collect AEs, concomitant medication and gout flare information (See 9.3.3.1.1).

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

- Investigator Assessment of Clinical Status.
- Document gout flares and intensity.
- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate including the measurement of weight. (see Section 9.5.4.4).
- Collect swollen/tender joint counts; administer HAQ; and record patient and physician global assessments and joint pain assessment responses.
- Assessment of Tophi.
- Assess MTX compliance.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis 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 uric acid:creatinine ratio.
- Obtain blood samples for pegloticase PK analysis.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies.
- Obtain a blood sample (1 sample) for measurement of sUA.
- Inquire about AEs and concomitant medication use.
- Perform DECT (if applicable). 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.

9.5.6.4 Week 52/End of Study/Early Termination Visit

- Investigator Assessment of Clinical Status.
- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.
- Assessment of Tophi.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, heart rate include measurement of weight. (see Section 9.5.4.4).
- Collect swollen/tender joint counts; administer HAQ; and record patient and physician global assessments and joint pain assessment responses.
- Assess MTX compliance.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Obtain a 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 uric acid:creatinine ratio.
- Obtain a blood sample (1 sample) for measurement of sUA.
- Obtain blood samples for pegloticase PK analysis.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies.
- Inquire about AEs and concomitant medication use.
- Perform DECT (if applicable). DECT may be completed within +/- 5 days of the scheduled visit.

9.5.6.5 Safety Follow-up Phone/Email/Site Visits

Thirty (30) days after the last MTX dose, subjects will be contacted by telephone or email or may visit the site to review 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.

9.5.6.6 MTX Partner Pregnancy Follow-up

Subjects who are non-vasectomized males, a phone/e-mail/site visit inquiry will be conducted 3 months after MTX discontinuation regarding partner pregnancy (this can be conducted at the 3 month Post Treatment Follow-up Visit).

9.5.6.7 Post Treatment Follow-up

The intent is for 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, heart rate and weight). (see Section 9.5.4.4).
- Perform a targeted physical examination should include heart, lungs and abdominal exam and joint and skin evaluation and assessment of AEs. Any finding will be recorded as an AE.

- Collect swollen/tender joint counts; administer HAQ; and record patient and physician global assessments and joint pain assessment responses.
- Assessment of Tophi.
- 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 prior to the infusion (3 Month Post Treatment Follow-up Visit only).
- Inquire about AEs and concomitant medication use.

9.6 Statistical Methods and Determination of Sample Size

Detailed statistical analyses will be presented in a separate statistical analysis plan (SAP). Some key points identified for statistical analyses are outlined below.

9.6.1 Endpoints

9.6.1.1 Primary Endpoint

The primary efficacy endpoint is the proportion of Month 6 (Weeks 20, 22, 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 are:

- 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, 22 and 24) combined.
- The proportion of 5 mg/dL responders during Month 3, during Month 6, and overall (Months 3 and 6 combined), defined as subjects achieving and maintaining sUA < 5 mg/dL for at least 80% of the time during each timepoint.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in sUA.

9.6.1.3 Exploratory Endpoints

The exploratory efficacy endpoints are:

- 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.

- 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.
- The proportion of Month 9 (Weeks 32, 34 and 36) 5 mg/dL responders, defined as subjects achieving and maintaining sUA <5 mg/dL for at least 80% of the time during Month 9.
- The proportion of Month 12 (Weeks 48, 50 and 52) 5 mg/dL responders, defined as subjects achieving and maintaining sUA <5 mg/dL for at least 80% of the time during Month 12.
- The time to first sUA > 6 mg/dL.
- The time to two consecutive sUAs > 6 mg/dL (stopping rule).
- The mean change from baseline to Weeks 24, 36, and 52 in urate volume and bone erosions due to gout using DECT.
- The mean change from baseline in number of joints affected by tophi
- The mean change from baseline to Weeks 14, 24, 36, and 52 in tender joint count (68 point scale).
- The mean change from baseline to Weeks 14, 24, 36, and 52 in swollen joint count (66 point scale).
- The mean change from baseline to Weeks 14, 24, 36, and 52 in HAQ-DI.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in HAQ pain score.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in HAQ health score.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in patient global assessment of gout.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in physician global assessment of gout.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in subject assessment of average, least, and worst joint pain.
- The proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36, and 52.

9.6.1.4 Pharmacokinetic and Anti-drug Antibody Endpoints

The PK and anti-drug antibody endpoints are:

- PK of pegloticase in subjects receiving concomitant MTX.
- Incidence of anti-PEG and anti-Uricase IgG antibodies.

9.6.1.5 Safety and Tolerability Endpoints

Safety and tolerability endpoints are:

- Incidence of IRs, anaphylaxis, gout flares, cardiovascular events, and the AE/SAE profile overall, and potentially attributed to the combination of pegloticase and MTX.

9.6.2 Populations for Analysis

The following analysis populations will be defined for this study:

- Intent-to-treat (ITT) population: all subjects who take at least one dose of MTX
- Modified intention-to-treat (mITT) population: all subjects who receive at least 1 dose of pegloticase
- Pharmacokinetic (PK) population: all subjects who receive at least 1 dose of pegloticase and have a post-pegloticase sample evaluable for PK analysis

9.6.3 Demographic Variables

Demographic data, including age, race, and gender, medical history, and other disease characteristics, will be summarized using descriptive statistics. Summaries of demographic variables will be provided for the ITT and mITT populations. Listings will include all screened subjects.

9.6.4 Subject Disposition

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 analysis population.

9.6.5 Efficacy Endpoint Analysis

Efficacy analyses will be performed using the mITT and ITT populations. There will be no statistical testing. 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. Additional details will be provided in the SAP.

9.6.5.1 Primary and Secondary Endpoint Analysis

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 Month 6 (Weeks 20, 22, and 24) 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. The proportion of responders will be summarized, along with a 95% exact (Clopper-Pearson) confidence interval for the proportion. The proportion of Month 3, overall (Months 3 and Month 6 combined), and 5 mg/dL responders (during Month 3, Month 6, and overall) will be summarized similarly.

A subject will be declared a non-responder if the subject had sUA level > 6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit. In addition, a subject who withdraws from the study for any reason (other than stopping rule) after the first dose of pegloticase in the pegloticase + IMM Period and prior to or during Month 6 (for the primary endpoint) or Months 3 or 6 (for the secondary endpoints) will be considered a non-responder if sUA values are not collected at planned timepoints.

sUA will be summarized at each visit and change from baseline to each visit with descriptive statistics.

9.6.5.2 Exploratory Endpoint Analysis

Swollen/tender joint counts, HAQ scores, patient and physician global assessment scores, and subject assessment of joint pain scores will be summarized at each visit along with changes from baseline using descriptive statistics.

The proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria will be calculated based on improvement in each of the components and summarized at Weeks 14, 24, 36 and 52. The proportion of responders at Month 9 and Month 12 will be summarized in a similar manner as the primary and secondary responder endpoints.

For subjects with DECT scans, the urate volume and bone erosion due to gout at each visit and changes from baseline will be summarized using descriptive statistics.

9.6.6 Pharmacokinetic and Anti-drug Antibody Analysis

Concentrations of 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 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 (whichever is later). TEAEs during the MTX Run-in Period will be summarized with the ITT population, and TEAEs during the Pegloticase + IMM Period will be summarized with both the ITT and mITT populations. TEAEs during any period (MTX Run-in Period or Pegloticase + IMM Period) will be summarized for the mITT population. AEs that occur more than 30 days after the last dose of pegloticase and/or 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 pegloticase

will also be provided. SAEs and AEs leading to discontinuation of MTX and pegloticase will be presented by system organ class and preferred term.

Incidence of IRs, gout flares, and other AEs of special interest will be summarized.

Laboratory test results, including urine uric acid: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 Run-in Period and Pegloticase + IMM Period will be summarized separately, where applicable.

9.6.8 Interim Analyses

No formal interim analysis is planned for this study. Efficacy and safety data may be summarized after all subjects enrolled in the study have completed the Week 14 visit or discontinued, and after all subjects have completed Week 24 or discontinued. Additional summary of the data may be performed periodically throughout the study, and safety data will be summarized regularly for safety monitoring. Final analysis will occur when all subjects have completed the study.

9.6.9 Sample Size and Power Considerations

A sample size of approximately 12-16 subjects is planned for this study. The primary efficacy endpoint, the proportion of subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6 (Weeks 20, 22, and 24) of the Pegloticase + IMM Period, will be demonstrated to be statistically greater than 43.5% (proportion of responders during Month 6 in phase 3 studies), according to an exact test for proportions with a 5% type I error, if at least 10/13 (77%) responders are observed; in that case, the lower bound of a 95% confidence interval for the proportion of responders will be about 46%.

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.

The Sponsor's Medical Monitor will consider any requests for exceptions to protocol entry criteria on a case-by-case basis. The Investigator or other health professional in attendance must contact the Sponsor as soon as possible. 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	[redacted]
Sponsor Representative	[redacted]
Sponsor Contact for Serious Adverse Event Reporting	[redacted]
24-hour Phone Contact for Safety Coverage	[redacted]

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

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Subject Number: _____ Date: _____

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING & GROOMING				
Are you able to:				
Dress yourself, including shoelaces and 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 own 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 the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.)
☐ Built up or special utensils
☐ Crutches
☐ Cane
☐ Wheelchair
☐ Special or built up chair
☐ Walker

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

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
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 above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
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 yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Long-handled appliances for reach

☐ Bathtub seat ☐ Long-handled appliances in bathroom ☐ Jar opener (for jars previously opened)

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

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

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY	MOSTLY	MODERATELY	A LITTLE	NOT AT ALL
☐	☐	☐	☐	☐

Your PAIN: How much pain have you had IN THE PAST WEEK?
On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain"), please record the number below.

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health), please record the number below.

17.3 Patient Global Assessment

PATIENT GLOBAL ASSESSMENT

"Considering all the ways that gout affects you, circle the number below that best represents how your gout has affected you over the last week",

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

17.4 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

17.5 Joint Pain Assessment

JOINT PAIN ASSESSMENT

Subject Assessments of Average Pain, Least Pain, and Worst Pain

Rate the AVERAGE PAIN you have had in your joints over the last week, by circling one of the numbers on the following 0 – 10 scale

0	1	2	3	4	5	6	7	8	9	10
No Joint Pain										Worst Possible Joint Pain

Rate the LEAST PAIN you have had in your joints over the last week, by circling one of the numbers on the following 0 – 10 scale

0	1	2	3	4	5	6	7	8	9	10
No Joint Pain										Worst Possible Joint Pain

Rate the WORST PAIN you have had in your joints over the last week, by circling one of the numbers on the following 0 – 10 scale

0	1	2	3	4	5	6	7	8	9	10
No Joint Pain										Worst Possible Joint Pain

17.6 Subject-Facing Diagram