CLINICAL TRIAL PROTOCOL FOR PEGLOTICASE

IND: 010122

Protocol Number: HZNP-KRY-407

Version 2.0, Amendment 1.0, Administrative Change 1.0

A Phase 4, Multicenter, Open-label, Efficacy and Safety Trial of Pegloticase and Methotrexate Co-administered in Patients with Uncontrolled Gout who have Previously Received Pegloticase Monotherapy but did not Maintain a Serum Uric Acid Response (ADVANCE)

Date: 02 May 2022

Sponsor:

Horizon Therapeutics Ireland DAC
70 St. Stephen's Green
Dublin 2 Ireland D02 E2X4

PROTOCOL

1 TITLE PAGE

Trial Title: A Phase 4, Multicenter, Open-label, Efficacy and Safety Trial of Pegloticase and Methotrexate Co-administered in Patients with Uncontrolled Gout who have Previously Received Pegloticase Monotherapy but did not Maintain a Serum Uric Acid Response (ADVANCE)

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Investigational Products: Pegloticase (recombinant modified mammalian urate oxidase [uricase]); methotrexate (MTX)

Indication: Chronic gout in adult patients refractory to conventional therapy

Sponsor: Horizon Therapeutics Ireland DAC
70 St. Stephen's Green
Dublin 2 Ireland D02 E2X4

Development Phase: 4

Sponsor's Responsible Medical Officer: PPD
Horizon Therapeutics U.S.A., Inc.
Two Tower Place, 12th Floor
South San Francisco, CA 94080

Sponsor Signatory: PPD
Horizon Therapeutics U.S.A., Inc.
Two Tower Place, 12th Floor
South San Francisco, CA 94080

Approval Date: 02 May 2022

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 trial, 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 contacts provided below.

Fax: PPD
Email: clinicalsafety@horizontherapeutics.com

SPONSOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-407

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Version Date: 02 May 2022

Approved by:

DocuSigned by:
PPD
Horizon Therapeutics U.S.A., Inc.

PPD
Date

DocuSigned by:
PPD
Horizon Therapeutics U.S.A., Inc.

PPD
Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-407

Version: 2.0, Amendment 1.0, administrative change 1

, Protocol Title: A Phase 4, Multicenter, Open-label, Efficacy and Safety Trial of Pegloticase and Methotrexate Co-administered in Patients with Uncontrolled Gout who have Previously Received Pegloticase Monotherapy but did not Maintain a Serum Uric Acid Response (ADVANCE)

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I agree to conduct the trial 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 trial drug supplied by the Sponsor will be used only as described in the protocol named above.

Signature:

_____ _____

Name Date
Trial Center
Address
City State Country

SUMMARY TABLE OF CHANGES
Protocol Version 2.0, Amendment 1 (10 August 2021) to Protocol Version 2.0, Amendment 1, Administrative change 1

The table below highlights the primary changes to the document. Track changes version of the Protocol Version 2.0, Amendment 1, Administrative change 1, can be provided on request.

Text **Version 2.0, Amendment 1** **10 August 2021**	**Amended Text** **Version 2.0, Amendment 1, Admin change 1** **02 May 2022**	**Reason for Change**
Approval Date 10 Aug 2021	**02 May 2022**	**Date of protocol approval**
Sponsor Address: 1 Burlington Road, Connaught House, 1st Floor, Dublin, Ireland, D04 C5Y	70 St. Stephen's Green, Dublin 2 , Ireland D02 E2X	Sponsor Address
Sponsor Medical Officer Address: 1 Horizon Way, Deerfield, IL 60015	Two Tower Place, 12th Floor South San Francisco, CA 94080	Sponsor Medical Officer address
Handheld Uric Acid Device Measurement: Synopsis; Protocol Section 9.5.1.1 All trial sites will be provided with Food and Drug Administration-approved handheld sUA devices to allow subjects to measure uric acid levels based on capillary samples	Text removed	The Handheld Device will not be used for this trial due to the unavailability of the control solution for the calibration of the device.
Schedule of Assessment Handheld Device Training, Handheld Device measurement: Footnote #20.	References removed.	Reason as above
Handheld Uric Acid Device Measurement: Protocol Section 9.5.1.1	Section removed	Reason as above

All trial sites and subjects will be provided with FDA-approved handheld sUA devices to measure subject uric acid levels based on capillary samples. Results will be collected in the eCRF at non-infusion visits and pre- and post-infusion during pegloticase infusion visits. Subjects may also use the device to measure uric acid at home. Results will be collected for exploratory uses only. No in-trial treatment decisions will be made based upon the data generated with the handheld device. In addition, user experience by Investigators or patients will be assessed by a uric acid device questionnaire at the Week 6, Week 12 and Week 24/End of Trial/Early Termination Visits.		
Section 9.5 Trial Procedures Day 1 and all subsequent visits If handheld uric acid device is provided, measure blood uric acid level at the same time point as blood sample collection for central laboratory sUA analysis.	**Text removed**	**Reason as above**
Section 9.5 Trial Procedures Day 1 , Week 4, 6, 8, 12, 14, 32,34, 44, 46 If handheld uric acid device is provided, measure blood uric acid level after the end of the pegloticase infusion (at least 1-hour post infusion) prior to discharge from the site.	**Text removed**	**Reason as above**
Section 9.5 Trial Procedures. Post infusion Day 1 – Week 12 If handheld uric acid device is provided, measure blood uric acid level at the same time point as blood sample collection for central laboratory sUA analysis.	**Text removed**	**Reason as above**
Sponsor Contact for DECT imaging BioClinica	Clario	Vendor name change

2 SYNOPSIS

Protocol Title: A Phase 4, Multicenter, Open-label, Efficacy and Safety Trial of Pegloticase and Methotrexate Co-administered in Patients with Uncontrolled Gout who have Previously Received Pegloticase Monotherapy but did not Maintain a Serum Uric Acid Response (ADVANCE)	
Protocol Number: HZNP-KRY-407	**Phase:** 4
Protocol Version: 2.0	
Test Drugs: KRYSTEXXA® (pegloticase); methotrexate (MTX)	**Indication**: Chronic gout in adult patients refractory to conventional therapy
Number and Country of Trial Sites: Approximately 10 to 15 trial sites in the United States	

Objectives:
The overall objective of this trial is to evaluate the efficacy and safety of pegloticase and MTX co-administered in subjects with uncontrolled gout who previously received pegloticase without a concomitant immunomodulator but did not maintain a serum uric acid (sUA) response (i.e., unable to maintain sUA <6 mg/dL while being treated with pegloticase alone and/or stopped pegloticase treatment due to an infusion reaction [IR]).

Primary Objective

The primary objective is to demonstrate that the response rate during Month 6 (Weeks 20, 21, 22, 23 and 24), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 6, is greater than 20% in subjects receiving pegloticase with MTX.

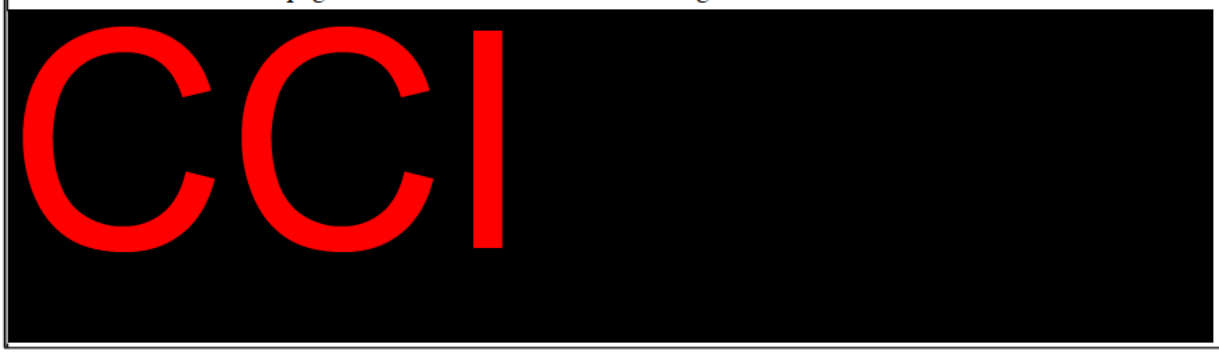
Secondary Objectives

To evaluate the effect of pegloticase with MTX on the following:

- 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.
- The proportion of subjects who experienced any of the following events from Day 1 to Week 24: IR leading to discontinuation of treatment, anaphylaxis or meeting Individual Subject sUA Discontinuation Criteria
- The change from Baseline in urate deposition volume, measured by dual-energy computed tomography (DECT) scan.
- The change from Baseline in Health Assessment Questionnaire (HAQ) - Disability Index (HAQ-DI) score.
- The change from Baseline in HAQ pain score.
- The change from Baseline in HAQ health score.

Exploratory Objectives

To evaluate the effect of pegloticase with MTX on the following:



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Safety and Tolerability Objectives

To evaluate the effect of pegloticase with MTX on the following:

- The adverse event (AE)/serious adverse event (SAE) profile overall for pegloticase and MTX and the incidence of adverse events of special interest (AESIs), including IRs, anaphylaxis, gout flares and major adverse cardiovascular events (MACE, defined as non-fatal stroke, non-fatal myocardial infarction, cardiovascular death and congestive heart failure).
- The change from Baseline in safety laboratory test results, including high-sensitivity C-reactive protein (hs-CRP).
- The change from Baseline in vital signs.

Trial Design

This is a Phase 4, multicenter, open-label trial of pegloticase with MTX in adult subjects with uncontrolled gout who were previously treated with pegloticase without a concomitant immunomodulator and stopped pegloticase due to failure to maintain sUA response and/or a clinically mild IR. Approximately 30 subjects will be enrolled. Pegloticase + MTX will be administered for approximately 24 weeks, with an optional extension up to 48 weeks.

The trial design will include 5 distinct components:

1) a Screening Period, lasting up to 42 days;
2) a 6-week MTX Tolerability Assessment Period (hereafter referred to as the MTX Run-in Period);
3) a 24-week Pegloticase + MTX Treatment Period, which will include a Week 24/End of Trial/Early Termination Visit (subjects that end MTX and pegloticase treatment prior to the Week 24 will remain on trial for follow up until the Week 24 visit);
4) an Optional Pegloticase + MTX Extension Period from Week 24 to Week 48, if a subject may gain further benefit with additional pegloticase treatment per the discretion of the Principal Investigator, which will include a Week 48/Optional End of Trial/Optional Early Termination Visit and
5) a 30-Day Post-Treatment Follow-up (Phone/Email) 30 days after the last pegloticase infusion or last dose of MTX (for subjects who are unable to tolerate MTX during the MTX Run-in Period and do not dose pegloticase). Subjects that end MTX and pegloticase treatment prior to Week 24 and remain on trial for at least 30 days prior to Week 24 will complete the 30-Day Post-Treatment Follow-Up as part of the visits following the End of Pegloticase visit.

All subjects who meet eligibility criteria at Screening will begin titrating up to a once-weekly subcutaneous (SC) MTX at a target dose of 25 mg (if the estimated glomerular filtration rate [eGFR] is ≥45 mL/min/1.73 m^2) or 15 mg (if eGFR is ≥30 and <45 mL/min/1.73 m^2) for 6 weeks prior to the first dose of pegloticase. Subjects will also take folic acid at a starting dose of 1 mg orally every day beginning at Week -6 (preferably 2 days prior to the first dose of MTX) continuing until prior to the End of Pegloticase (if applicable) or 1 week after the last pegloticase infusion for subjects who have not stopped pegloticase treatment. A higher folic acid dose or alternative folate supplement will be allowed (see Section 9.4.1.3 for specific instructions).

Subjects must be able to tolerate MTX at a minimum dose of 15 mg during the 6-week MTX Run-in Period to be eligible to participate in the Pegloticase + MTX Treatment Period, regardless of Baseline eGFR. Subjects who are unable to tolerate MTX 15 mg during the MTX Run-in Period will be considered MTX Run-in Screen Failures.

Female subjects of childbearing potential who inject at least 1 dose of MTX will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of MTX to verify that at least 1 ovulatory cycle has occurred since the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed.

For those subjects who inject at least 1 dose of MTX and who are non-vasectomized males, an inquiry will be made 3 months after the subject's last dose of MTX regarding partner pregnancy.

All subjects who meet the inclusion/exclusion criteria and complete the MTX Run-in Period will be considered enrolled subjects and will receive the first pegloticase infusion on Day 1. All subsequent doses and trial visits will be scheduled based on the Day 1 Visit date.

Prior to the Pegloticase + MTX Treatment Period, subjects will begin taking at least 1 standard gout flare prophylaxis regimen (i.e., colchicine and/or nonsteroidal anti-inflammatory drug and/or low-dose prednisone ≤10 mg/day) per protocol beginning ≥1 week before the first dose of pegloticase, continuing for at least 6 months per American College of Rheumatology guidelines (FitzGerald et al, 2020). For IR prophylaxis, fexofenadine (180 mg orally) and prednisone (50 mg orally) will be taken the night before each pegloticase infusion; fexofenadine (180 mg orally), famotidine (20 mg orally), montelukast (10 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each pegloticase infusion; methylprednisolone (125 mg intravenous [IV]), over an infusion duration between 10 and 30 minutes, will be administered prior to each pegloticase infusion.

During the Pegloticase + MTX Treatment Period, pegloticase 8 mg will be administered IV every 2 weeks from Day 1 through the Week 22/Week 46, after all predose trial visit assessments have been completed at each visit. The date, start and stop time of infusion will be recorded.

During the Pegloticase + MTX Treatment Period, subjects will be instructed to inject MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase infusion (on the weeks when pegloticase is administered); however, if a subject does not do so, MTX must be injected ≥60 minutes prior to each pegloticase infusion. One additional weekly dose of MTX will be injected after the last pegloticase infusion for subjects who have not stopped pegloticase due to individual subject sUA discontinuation criteria. If the subject discontinues pegloticase due to the stopping rule or other reason, MTX and folic acid should also be discontinued.

After Day 1, if a subject becomes unable to tolerate MTX, the folic acid dose can be increased, an alternative folate supplement may be used and/or the MTX dosage may be reduced or discontinued based on pre-defined criteria (Section 9.4.6.3.2.2) and the subject may remain in the trial and continue pegloticase infusions. Every attempt should be made to re-start the MTX in subjects once their MTX-associated symptoms have improved or their laboratory tests have normalized.

The Investigator will review the subject clinical status and CCI at Week -6; prior to pegloticase infusion at the Week 24 and Week 36 Visits (for subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period); and at the End of Pegloticase (if applicable) and 48/End of Trial/Early Termination Visits (if applicable).

After the Week 24 or 48 Visit (or End of Pegloticase Visit [if applicable]) or upon pegloticase discontinuation, subjects should resume regular care for gout per the judgment of the treating physician, including resumption of urate-lowering therapy, if appropriate.

Two sequential cohorts of subjects will be enrolled in this trial. Cohort 1 is targeted to enroll 10 subjects who previously failed to maintain sUA response with pegloticase monotherapy and stopped pegloticase treatment without a history of pegloticase-related IR. After 7 and 10 subjects (or more often if needed) in Cohort 1 complete at least 6 infusion visits, safety assessments of IR and anaphylaxis from available subjects' data will be performed by the Safety Review Team (comprising members of the Horizon Clinical Development and Patient Safety and Pharmacovigilance Teams) based on pre-determined tolerability criteria. If a subject discontinues treatment or discontinues the trial prior to the 7th infusion, their available data will be included in the safety assessment. If the safety assessment during Cohort 1 indicates that the pegloticase infusions are well tolerated based on the pre-determined criteria, then the trial can begin enrolling Cohort 2. If the safety assessment indicates that the pegloticase infusions are not well tolerated based on the pre-determined tolerability criteria (see tolerability criteria below), then the trial will cease to screen and enroll new subjects. Subjects who are ongoing and benefitting from continued treatment, as determined by the Principal Investigator at the time of the termination of new subject screenings, will be permitted to continue treatment and trial visits.

The aim is to enroll up to 20 subjects who failed to maintain sUA response with pegloticase monotherapy with or without a history of pegloticase-related clinically mild IR in Cohort 2. After 3, 6,10,15,and 20 subjects in Cohort 2 complete 6 infusion visits, safety assessments of IR and anaphylaxis from available subjects' data will

be performed by the Safety Review Team. If the safety assessment indicates that the pegloticase infusions are not well tolerated based on the pre-determined tolerability criteria (see tolerability criteria below) in subjects with a history of pegloticase-related clinically mild IR, the trial will continue with enrolling subjects without a history of pegloticase-related clinically mild IR to reach a total of 30 subjects enrolled for the trial.

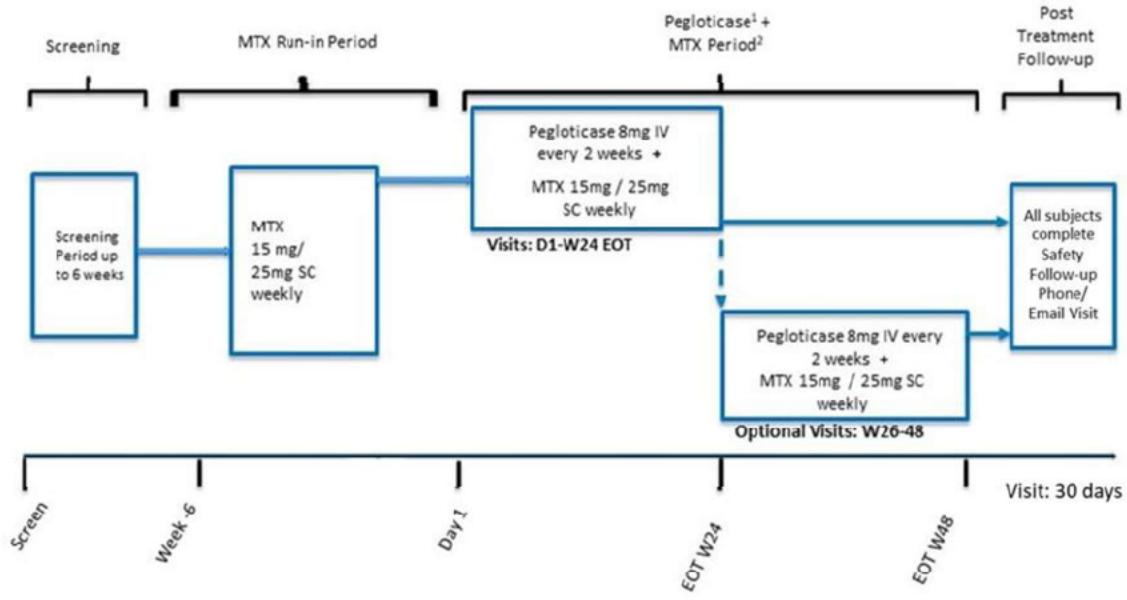
Depending on any potential safety signals reported (e.g., serious IR or any SAE related to pegloticase infusion), regular quarterly and/or ad hoc safety assessments will be conducted during the trial as specified in the Safety Management Plan and the Safety Review Team Charter. The regular quarterly reviews will include review of the database by the Safety Review Team and will be conducted as set out in the Safety Management Plan. The first safety review meeting will occur approximately after the first 3 subjects in Cohort 1 complete at least 12 weeks of the Pegloticase + MTX Treatment period (6 infusion visits). The Safety Review Team could stop the trial for other significant safety reasons.If 3 events of Anaphylaxis (as assessed by PI) occur an Adjudication Committee (composed of independent experts external to Horizon) will be established for this trial to adjudicate AESI's of Anaphylaxis. The committee will meet at a frequency defined in the Adjudication Committee Charter. The AESI of IR, MACE and gout flare will not be adjudicated.

Samples for measurement of sUA levels will be collected at Screening, during the MTX Run-in Period, prior to each infusion, additionally post-infusion on Day 1 and at the Week 10, 12, 14, 20, 22, 32, 34, 44 and 46 Visits and on non-infusion visits on the 1st (~24 hours), 4th (~96 hours), 7th (~168 hours) and 10th (~240 hours) day after the first 4 infusions (Infusions 1, 2, 3, 4) and on the 1st (~24 hours),and 7th (~168 hours) day after the , 5th , 6th and 7th infusions; Day 1 through prior to Week 14) (see objectives for these frequent sUA measurements in the Individual Subject sUA Discontinuation Criteria section below), Weeks 21 and 23, and at the End of Pegloticase (if applicable) or the Week 24 or 48/End of Trial/Early Termination Visit.

Samples will be collected for CCI [redacted] CCI [redacted] as indicated in Section 2.1 (Schedule of Assessments).

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 and urine test, will be performed.

An overview of the trial design is presented in the schematic below, and the details of the trial activities are provided in Section 2.1 (Schedule of Assessments).



D = Day; EOT = End of Trial; IV = intravenous; MTX = methotrexate; SC = subcutaneous; sUA = serum uric acid; W = Week

1 Individual subjects who meet the sUA discontinuation criteria will end pegloticase therapy, complete the End of Trial procedures and remain in the trial.

2	Key efficacy and safety assessments will be conducted during Weeks 10, 12, 14, 20, 21, 22, 23 and 24.

Subject Population:

Subjects diagnosed with gout who are unable to maintain sUA <6 mg/dL while being treated with pegloticase alone and/or stopped pegloticase treatment due to an IR or who experienced intolerable side effects associated with current urate-lowering therapy or for whom xanthine oxidase inhibitor therapy is contraindicated are eligible for the trial. Subjects must have previously been treated with pegloticase without concomitant immunomodulation and stopped pegloticase due to failure to maintain sUA response and/or pegloticase-related clinically mild IR.

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 trial.
3. Adult men or women ≥18 years of age.
4. Uncontrolled gout, defined by the following criteria:
    - Hyperuricemia during the Screening Period, defined as sUA ≥6 mg/dL, and;
    - Failure to maintain normalization of sUA with xanthine oxidase inhibitors at the maximum medically appropriate dose or with a contraindication to xanthine oxidase inhibitor therapy based on medical record review or subject interview, and;
    - Symptoms of gout, including at least 1 of the following:
        - Presence of at least 1 tophus
        - Recurrent flares, defined as 2 or more flares in the 12 months prior to Screening
        - Presence of chronic gouty arthritis
5. Subject was previously treated with pegloticase without concomitant immunomodulation and stopped pegloticase due to failure to maintain sUA reduction response (had ≥1 sUA >6 mg/dL within 2 weeks post pegloticase infusion) and did not experience an IR (Cohort 1) and/or stopped pegloticase treatment due to pegloticase-related clinically mild IR (Cohort 2) (see guidance on assessment of IR symptoms and severity in Appendix 17.9). A Sponsor Adjudication Committee will review the signs, symptoms and treatment administered for the prior IR associated with pegloticase infusion before subjects with history of mild IR are enrolled.
6. Subject for whom the last pegloticase infusion occurred >6 months prior to Screening.
7. Willing to discontinue any oral urate-lowering therapy at least 7 days prior to Day 1 and remain off other urate-lowering therapy during the Pegloticase + MTX Treatment Period.
8. 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 pregnancy tests during Screening;
    - Subjects must agree to use 2 reliable forms of contraception during the trial, 1 of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started ≥1 full cycle prior to Week -6 (start of MTX) and continue for 30 days after the last dose of pegloticase, or at least 1 ovulatory cycle after the last dose of MTX (whichever is the longer duration after the last dose of pegloticase). 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.
9. Men who are not vasectomized must agree to use appropriate contraception so as to not impregnate a female partner of reproductive potential during the trial, beginning with the initiation of MTX at Week -6 and continuing for at least 3 months after the last dose of MTX.

10. Able to tolerate MTX at SC doses of at least 15 mg during the MTX Run-in Period, regardless of eGFR status.

Exclusion Criteria:

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

1. Known history of medically confirmed prior anaphylactic reaction.
2. Known history of moderate or severe IR (including but not limited to difficulty in breathing, hypotension, generalized urticaria, generalized erythema, angioedema and/or required treatment with IV steroids or epinephrine; see guidance on assessment of anaphylaxis/IR symptoms and severity in Appendix 17.9) or other SAEs related to pegloticase or any other pegylated product treatment.
3. Weight >160 kg (352 pounds) at Screening.
4. Any serious acute bacterial infection, unless treated and completely resolved with antibiotics at least 2 weeks prior to Week -6 Visit.
5. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis.
6. Current or chronic treatment with systemic immunosuppressive agents, such as MTX, azathioprine, cyclosporine, leflunomide, cyclophosphamide or mycophenolate mofetil.
7. Current treatment with prednisone >10 mg/day or equivalent dose of another corticosteroid on a chronic basis (defined as 3 months or longer).
8. Known history of any solid organ transplant surgery requiring maintenance immunosuppressive therapy.
9. Known history of hepatitis B virus surface antigen positivity or hepatitis B DNA positivity, unless treated, viral load is negative and no chronic or active infection confirmed by hepatitis B virus serology.
10. Known history of hepatitis C virus RNA positivity, unless treated and viral load is negative.
11. Known history of human immunodeficiency virus positivity.
12. Glucose-6-phosphate dehydrogenase deficiency (tested at the Screening Visit).
13. Severe chronic renal impairment (eGFR <30 mL/min/1.73 m^2) at the Screening Visit based on 4 variable Modification of Diet in Renal Disease formula or currently on dialysis.
14. Non-compensated congestive heart failure, hospitalization for congestive heart failure or treatment for acute coronary syndrome (myocardial infarction or unstable angina) within 3 months of the Screening Visit, current uncontrolled arrhythmia or current uncontrolled blood pressure (>160/100 mmHg) prior to Week -6.
15. 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.
16. Prior treatment with another recombinant uricase (rasburicase) or concomitant therapy with a PEG-conjugated drug (see Appendix 17.10 for list of PEG-conjugated drugs).
17. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product.
18. Contraindication to MTX treatment or MTX treatment considered inappropriate.
19. Known intolerance to MTX.
20. Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to MTX administration at Week -6 or plan to take an investigational drug during the trial.

21. Current liver disease, as determined by alanine transaminase or aspartate transaminase >1.25 × upper limit of normal or albumin <lower limit of normal at the Screening Visit.
22. Currently receiving systemic or radiologic treatment for ongoing cancer, excluding non-melanoma skin cancer.
23. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix.
24. White blood cell count $<4.0 \times 10^9$/L, hematocrit <32% or platelet count $<75 \times 10^9$/L.
25. Diagnosis of osteomyelitis.
26. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
27. Unsuitable candidate for the trial (e.g., cognitive impairment), based on the opinion of the Investigator, 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 trial.
28. Alcohol use in excess of 3 alcoholic beverages per week.
29. A known intolerance to all protocol standard gout flare prophylaxis regimen (i.e., unable to tolerate any of the following 3 agents: colchicine, nonsteroidal anti-inflammatory drugs or low- dose prednisone ≤10 mg/day).
30. Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest x-ray may be performed during Screening.

Dose Regimen/Route of Administration:

MTX:

During the MTX Run-in Period, which begins 6 weeks prior to the first dose of pegloticase, subjects with eGFR ≥45 mL/min/1.73 m^2 will inject SC MTX weekly at a starting dose of 15 mg at Weeks -6 and Week -5 increasing to 25 mg at Week -4 and continuing weekly throughout the trial. Subjects with eGFR ≥30 and <45 mL/min/1.73 m^2 will inject SC MTX weekly at a starting dose of 10 mg at Week -6 and Week -5 increasing to 15 mg at Week -4 and continuing weekly throughout the trial. If a subject becomes unable to tolerate MTX at 25 mg doses, the folic acid dose may be increased from 1 to 2 mg/day and/or the MTX dosage may be decreased to 20 or 15 mg, but to no less than 15 mg. Subjects who cannot tolerate MTX at a minimum dose of 15 mg during the MTX Run-in Period will be considered MTX Run-in Screen Failures, regardless of their Baseline eGFR.

Subjects will be instructed to inject MTX weekly on the same day each week and record the date, time and mg dose of each dose in the dosing calendar (see RASUVO Full Prescribing Information). Since subjects should inject MTX within 1 to 3 days prior to pegloticase infusions beginning at Day 1, the Investigator should consider which day of the week to request the subject dose MTX such that the MTX dose will align with within 1 to 3 days prior to pegloticase infusions which will begin at Day 1.

During the MTX Run-in Period, if a dose is missed, it should be injected 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. If a subject misses more than 2 doses of MTX during the 6-week Run-in Period, the Principal Investigator should contact the Sponsor to discuss eligibility of the subject for enrollment in the Pegloticase + MTX Treatment Period.

During the Pegloticase + MTX Treatment Period, MTX should be injected 1 to 3 days prior to the pegloticase infusion and 1 additional weekly dose should be injected after the last pegloticase infusion with the exception of subjects who have not stopped pegloticase due to trial sUA discontinuation rule. If a subject is not able to inject MTX 1 to 3 days prior to the pegloticase infusion, MTX must be injected ≥60 minutes prior to the pegloticase infusion.

During the Pegloticase + MTX Treatment Period, if a subject becomes unable to tolerate MTX, the folic acid dose may be increased, an alternative folate supplement may be used and/or the MTX dosage may be decreased (see Section 9.4.6.3.2.2 for detailed instructions).

Subjects will also take folic acid at a starting dose of 1 mg orally every day beginning at Week -6 (preferably 2 days before the start of MTX) until 1 week after the last pegloticase infusion for subjects who have not stopped pegloticase treatment.

Pegloticase:

All subjects who meet the inclusion/exclusion criteria and tolerate SC MTX at a minimum dose of 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 12 infusions from Day 1 through Week 22 inclusive, or a total of up to 24 infusions from Day 1 through Week 46, inclusive, for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement (Optional Pegloticase + MTX Extension Period). The date, 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 continuing for at least 6 months per American College of Rheumatology guidelines (FitzGerald et al, 2020). Standardized IR prophylaxis consisting of pre-treatment with antihistamines, acetaminophen, a leukotriene inhibitor and corticosteroids will accompany each infusion.

Dosage Form and Strength Formulation (Pegloticase and MTX):

Pegloticase will be supplied as KRYSTEXXA®, which 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 for IV infusion by gravity feed or infusion pump, generally over 120 minutes. Pegloticase will not be administered as an IV push or bolus.

MTX for SC injection in auto-injectors (7.5, 10, 15, 20, 25 mg) will be provided to all subjects (see RASUVO Full Prescribing Information). For each subject, the MTX dose will be based on their Baseline eGFR value.

Duration of Treatment and Follow-up:

Screening. Up to 42 days prior to the Pegloticase + MTX Treatment Period.

MTX Run-in Period (Week -6 to Day 1). 6 weeks (6 doses) of MTX dosing prior to initial pegloticase dose.

Pegloticase + MTX Treatment Period (Day 1 through Week 24). 22 weeks (infusion visits every 2 weeks/12 infusions) plus the End of Trial (Week 24)/Early Termination Visit.

End of Pegloticase Visit (if applicable). If the subject discontinues pegloticase treatment prior to Week 22, such as due to the sUA Discontinuation Criteria, the subject will complete this visit within approximately 2 weeks of the last infusion. Subjects will continue on trial without infusion for the remainder of trial visits, including the 30-Day Post-Treatment Follow-up and Week 24/End of Trial/Early Termination Visits. For subjects who agree to continue trial visits after the End of Pegloticase Visit, the 30-Day Post-Treatment Follow-up Visit will be captured as part of the continued visits; however, if the last trial visit is <30 days posttreatment, the 30-Day Post-Treatment Follow-up phone call/email will still be required.

Optional Pegloticase + MTX Extension Period (Week 24 through Week 48). For subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement, an Optional Pegloticase + MTX Extension Period, from Week 24 to Week 48, can be added.

30-Day Post-Treatment Follow-up Visit (30 days post last pegloticase infusion). All subjects will receive a safety follow-up phone call/e-mail/visit approximately 30 days after the last dose of MTX or the final infusion of pegloticase, whichever occurs last. Subjects who receive at least 1 dose of MTX and are females of childbearing potential, will receive a safety follow-up phone call/e-mail approximately 4 weeks/30 days after the last dose of MTX to verify at least 1 ovulatory cycle has occurred after the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed.

MTX Partner Pregnancy Follow-up. Subjects who receive at least 1 dose of MTX and are non-vasectomized males will receive a phone call/e-mail inquiry 3 months after MTX discontinuation regarding partner pregnancy.

Restricted Medications

Subjects will be directed to discontinue current urate-lowering therapy for at least 7 days prior to Day 1.

The following medications are prohibited from Screening through the end of pegloticase and MTX during the trial:

- Concomitant therapy with allopurinol, febuxostat, probenecid or other urate-lowering medications or a PEG-conjugated drug.
- Other investigational agents.
- Any MTX other than the trial approved investigational product, azathioprine, mycophenolate mofetil or other systemic immunosuppressants aside from glucocorticoid for gout flare or IR prophylaxis or intermittent gout flare treatment.
- Systemic or radiologic treatment for ongoing cancer, excluding non-melanoma skin cancer.
- Current or chronic treatment with systemic immunosuppressive agents.

Other medications used at the time of trial initiation may be continued at the discretion of the Investigator.

Removal of Subjects from Treatment or Assessment

Every effort should be made to retain a subject in the trial to monitor their safety. Subjects who are removed from pegloticase therapy should remain in the trial unless they withdraw consent. However, subjects may withdraw consent or discontinue treatment or participation from the trial at any time, without prejudice to further treatment. In addition, the Investigator may terminate a subject's treatment at any time. The primary reason for discontinuation from the trial and/or trial drug should be recorded on the electronic case report form.

Criteria for Evaluation:

Efficacy will be assessed by sUA levels, urate deposition volume and CCI [redacted] CCI [redacted], CCI [redacted] and HAQ-DI, Health Assessment Questionnaire (HAQ) pain scale and HAQ health scale.

CCI [redacted]

The CCI [redacted] 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 and urine test.

Tolerability Criteria:

Safety assessments of IR and anaphylaxis will be conducted after 7 and 10 subjects in Cohort 1 complete 6 infusions and after 3, 6, 10, 15, and 20 subjects in Cohort 2 complete 6 infusions. If more than one-third of subjects experience a severe IR and/or anaphylaxis related to pegloticase infusion, the pegloticase infusions will be considered not tolerated.

The signs and symptoms of severe IRs are usually prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion) or recurrent following initial improvement. Possible associated signs and symptoms of IRs may include, but not be limited to:

- Respiratory: difficulty breathing with wheezing or stridor; respiratory distress manifested as at least 2 or more of the following: tachypnoea, increased use of accessory respiratory muscles, cyanosis, recession or grunting;
- Upper airway swelling (lip, tongue, throat, uvula or larynx);
- Cardiovascular: hypertension, tachycardia, measured hypotension, a decreased level of consciousness or loss of consciousness; and

- Dermatological or mucosal: generalized urticaria (hives), generalized erythema, angioedema or generalized pruritus with skin rash.

The Safety Review Team must confirm that the tolerability criteria are not met in Cohort 1, prior to Screening subjects with history of pegloticase-related mild IR for Cohort 2. The Safety Review Team could stop the trial for other significant safety concerns.

If a confirmed anaphylaxis event occurs in any subject, further dosing with pegloticase for that subject will be discontinued. Anaphylaxis events will be adjudicated using the Sampson criteria (see Appendix **Error! Reference source not found.** for guidance on anaphylaxis and IR symptoms and assessment).

Individual Subject sUA Discontinuation Criteria:

Individual subject sUA will be measured locally within 48 hours prior to each pegloticase infusion throughout the trial and by the central laboratory on infusion visit days.

In addition, sUA will be collected between infusions for the first 12 weeks of the trial. These interim sUA values will be measured after the first 4 infusions at the 1st (~24 hours), 4th (~96 hours), 7th (~168 hours) and 10th (~240 hours) day after each infusion. For infusion 5, 6, 7, the interim sUA values will be measured at the 1st (~24 hours) and 7th (~168 hours) day after each infusion.

Pegloticase treatment will continue if there is a meaningful sUA reduction from the Baseline, at the discretion of the Principal Investigator, even if sUA<6 mg/dL is not maintained consistently over the 2-week interval between infusions during this 12-week period. However, pegloticase treatment should be stopped if the lowest available interim sUA value (typically the 1st day [~24 hours] after infusion) after the pegloticase infusion at Week 2, 4, 6, 8, 10 or 12 is less than a 50% reduction from the highest sUA value measured between Screening and pre-infusion on Day 1.

Prior to Week 22, subjects who discontinue treatment due to individual subject sUA levels, as evaluated by the Principal Investigator, will remain in the trial for biweekly visits, including the Week 24/End of Trial/Early Termination and 30-Day Post-Treatment Follow-up Visits if not captured as part of post treatment follow up.

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Statistical Analyses:

Primary Endpoint

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

Secondary Endpoints

- The proportion of Month 3 (Weeks 10 to 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 subjects who experienced any of the following events from Day 1 to Week 24: IR leading to discontinuation of treatment, anaphylaxis or meeting Individual Subject sUA Discontinuation Criteria.
- The mean change from Baseline in urate deposition volume (measured by DECT) to Week 24.
- The mean change from Baseline in HAQ-DI score at Weeks 14 and 24.
- The mean change from Baseline in HAQ pain score at Weeks 14 and 24.
- The mean change from Baseline in HAQ health score at Weeks 14 and 24.

Exploratory Endpoints

CCI Endpoints

- The concentrations of CCI over time.
- The incidence and titer of CCI over time.
- The concentrations of CCI over time.

Safety and Tolerability Endpoints

- The incidence of IRs, anaphylaxis, gout flares, MACE and the AE/SAE profile overall and potentially attributed to the combination of pegloticase and MTX.
- The mean change from Baseline in laboratory test results, including hs-CRP.
- The mean change from Baseline in vital sign results.

Statistical Analysis on Efficacy and Safety Parameters

The estimand for the primary analysis will use the Treatment Policy Strategy for most intercurrent events; selected intercurrent events leading to data that are missing completely at random may be addressed with a While-on-Treatment Strategy (e.g., if site closures due to coronavirus disease 2019 [COVID-19]).

The number of subjects treated, the number of doses administered and the reason for discontinuing treatment will be summarized, along with demographic and Baseline characteristics.

The primary efficacy endpoint is the proportion of responders during Month 6. The proportion of time each subject's sUA is <6 mg/dL will be calculated using observed data at Weeks 20, 21, 22, 23 and 24. The amount of time that sUA is <6 mg/dL (using linear interpolation, if necessary) will be calculated and divided by the total amount of time from the first to the last observed sUA value in this time range (missed values in this time range will be ignored for purposes of this calculation). Subjects who have no available sUA value in this time range will be imputed as non-responders unless the data are missing completely at random, in which case they will be omitted from the analysis. Two-sided exact 95% confidence intervals (CIs) will be calculated.

The primary analysis will be performed on all enrolled subjects who receive ≥1 dose of pegloticase.

The proportion of Month 3 responders will be summarized similarly to the Month 6 responders. All sUA results collected between infusions from Week 10 through Week 14 of the trial will be used in the calculation of the Month 3 responders.

The mean change from Baseline in urate deposition volume (measured by DECT) to Week 24 will be summarized along with the corresponding 95% CI for subjects with DECT assessments.

The proportion of subjects experiencing any of the following events: IR leading to discontinuation of treatment, anaphylaxis or meeting Individual Subject sUA Discontinuation Criteria will be presented. For this composite endpoint, each individual component of the composite will be analyzed with a summary of the incidence and the corresponding 95% CI.

The primary and secondary endpoints will be summarized overall and by cohort. If Cohort 2 enrolls both subjects with previous mild IR and those with no previous IR, then the data will be summarized by IR category (no IR,

mild IR) within Cohort 2 and for Cohorts 1 and 2 combined. No adjustments to CIs will be made for multiple endpoints or multiple time points.

The number and percentage of subjects with at least 1 AE, at least 1 SAE, at least 1 severe AE and with an AE that leads to discontinuation of pegloticase and/or MTX will be summarized. Adverse events will be listed.

The impact of CCI, efficacy (responder rate) and safety (IR) will be explored.

Sample Size Estimate:

A sample size of 30 subjects is planned for this trial to provide a sizeable number of subjects to support the following projections. The primary efficacy endpoint will be demonstrated to be statistically greater than 20% if at least 12/30 (40%) responders are observed. In that case, the lower bound of a 95% CI for the proportion of responders will be approximately 23%.

2.1 Schedule of Assessments

	Screening[1]	MTX Run-in Period[2]			Pegloticase + MTX Treatment Period[3] Day 1 through Week 24 EOT															Optional Extension to Wk 48
						Week (±3 d)														
	Screening Visit	(-6 wks ±3 d)	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 21	End of Pegloticase Visit[4] (if applicable)	Wk 22	Wk 23	Wk 24/ EOT*	Wk 24 (±3 d)
Trial Procedure/ Assessment					Inf: 1	Inf: 2	Inf: 3	Inf: 4	Inf: 5	Inf: 6	Inf: 7	Inf: 8	Inf: 9	Inf: 10	Inf: 11		Within 2 wks following final infusion	Inf: 12			Inf: 13
Informed consent	X																				
Enrollment					X																
Demographic data	X																				
Inclusion/exclusion criteria	X	X	X	X	X																
Medical/surgical history[5]	X																				
Medication/ substance use history[6]	X																				
Chest x-ray	X																				
Physical examination[7]	X			X	X		X		X		X		X		X		X			X	X
Vital signs, height[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X
Weight[9]	X				X												X			X	X
Electrocardiogram[10]	X																				
AE/SAE assessment[11]	X	X	X	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 + MTX Treatment Period[3] Day 1 through Week 24 EOT															Optional Extension to Wk 48
					Week (±3 d)															
	Screening Visit	(-6 wks ±3 d)	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 21	End of Pegloticase Visit[4] (if applicable)	Wk 22	Wk 23	Wk 24/ EOT*	Wk 24 (±3 d)
Trial Procedure/ Assessment					Inf: 1	Inf: 2	Inf: 3	Inf: 4	Inf: 5	Inf: 6	Inf: 7	Inf: 8	Inf: 9	Inf: 10	Inf: 11		Within 2 wks following final infusion	Inf: 12			Inf: 13
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Document gout flares and intensity	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI		X			X			X				X			X		X			X	X
HAQ-DI		X			X			X				X			X		X			X	X
CCI		X			X							X					X			X	X
CCI		X			X							X					X			X	X
CCI		X			X							X					X			X	X
CCI		X			X							X					X			X	X
DECT[12]		X										X					X			X	X
MTX dosing calendar		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
MTX dispensed[13]		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X*			X
MTX dosing		Once weekly from Week -6 to Week 23 Visit, inclusive																			X
Folic acid Rx filled[14]		Rx filled as needed																			X
Gout prophylaxis Rxs filled[15]				Rxs filled as needed																	X

	Screening[1]	MTX Run-in Period[2]			Pegloticase + MTX Treatment Period[3] Day 1 through Week 24 EOT															Optional Extension to Wk 48
					Week (±3 d)															
	Screening Visit	(-6 wks ±3 d)	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 21	End of Pegloticase Visit[4] (if applicable)	Wk 22	Wk 23	Wk 24/ EOT*	Wk 24 (±3 d)
Trial Procedure/ Assessment					Inf: 1	Inf: 2	Inf: 3	Inf: 4	Inf: 5	Inf: 6	Inf: 7	Inf: 8	Inf: 9	Inf: 10	Inf: 11		Within 2 wks following final infusion	Inf: 12			Inf: 13
IR prophylaxis Rxs filled[16]				Rxs filled as needed																X
MTX compliance/ reconciliation			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X
IR prophylaxis[16] and compliance (Yes/No)					X	X	X	X	X	X	X	X	X	X	X			X			X
Folic acid compliance (Yes/No)			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X
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
CCI [redacted]					X	X		X				X					X	X		X	X
CCI [redacted]		X			X	X		X				X					X	X		X	X
Pre-infusion CCI [redacted] sampling					X							X						X		X	X
sUA[19]	X	X		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 + MTX Treatment Period[3] Day 1 through Week 24 EOT															Optional Extension to Wk 48
					Week (±3 d)															
	Screening Visit	(-6 wks ±3 d)	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 21	End of Pegloticase Visit[4] (if applicable)	Wk 22	Wk 23	Wk 24/ EOT*	Wk 24 (±3 d)
Trial Procedure/ Assessment					Inf: 1	Inf: 2	Inf: 3	Inf: 4	Inf: 5	Inf: 6	Inf: 7	Inf: 8	Inf: 9	Inf: 10	Inf: 11		Within 2 wks following final infusion	Inf: 12			Inf: 13
sUA[19] (central)/blood					1st (~24 hr), 4th (~96 hr), 7th (~168 hr) and 10th (~240 hr) day after infusions 1, 2, 3, 4 1st (~24 hr), and 7th (~168 hr) day after infusions 5, 6 and 7																
Hematology	X			X	X	X		X				X					X			X	X
Clinical chemistry	X			X	X	X		X				X					X			X	X
eGFR (calculated by the central laboratory)	X				X	X		X				X					X			X	X
Urine albumin: creatinine ratio	X				X	X		X				X					X			X	X
G6PD test[21]	X																				
hs-CRP	X				X							X					X			X	X
Additional samples for future analysis[22]		X			X							X					X			X	X
Pregnancy test[23]	X	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 + MTX Treatment Period[3] Day 1 through Week 24 EOT														Optional Extension to Wk 48
						Week (±3 d)													
	Screening Visit	(-6 wks ±3 d)	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 21	End of Pegloticase Visit[4] (if applicable)	Wk 22	Wk 23	Wk 24/ EOT*	Wk 24 (±3 d)
Trial Procedure/ Assessment					Inf: 1	Inf: 2	Inf: 3	Inf: 4	Inf: 5	Inf: 6	Inf: 7	Inf: 8	Inf: 9	Inf: 10	Inf: 11		Within 2 wks following final infusion	Inf: 12			Inf: 13
CCI [redacted]		X															X			X	X

Table footnotes and abbreviations are presented on the last page.

	Optional Pegloticase + MTX Extension Period (Week 26 through Week 46)											Wk 48/ EOT/ET	30-Day Post-Treatment Follow-up Visit[25]	MTX Partner Pregnancy Follow-up
	Week (±3 d)													
	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	Wk 36	Wk 38	Wk 40	Wk 42	Wk 44	Wk 46		~30 days after last pegloticase infusion or MTX dose (±3 d)	~3 months after last MTX dose
Trial Procedure/ Assessment	**Inf: 14**	**Inf: 15**	**Inf: 16**	**Inf: 17**	**Inf: 18**	**Inf: 19**	**Inf: 20**	**Inf: 21**	**Inf: 22**	**Inf: 23**	**Inf: 24**			
Physical examination[7]						X						X		
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X	X		
Weight[9]												X		
AE/SAE assessment[11]	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	
Document gout flares and intensity	X	X	X	X	X	X	X	X	X	X	X	X		
CCI [redacted]						X						X		
HAQ-DI						X						X		
CCI [redacted]						X						X		
CCI [redacted]						X						X		
CCI [redacted]						X						X		
CCI [redacted]						X						X		
DECT[12]												X		
MTX dosing calendar	X	X	X	X	X	X	X	X	X	X	X			
MTX dispensed[13]	X	X	X	X	X	X	X	X	X	X				
MTX dosing	Once weekly from Week 24 to the Week 47, inclusive													

	Optional Pegloticase + MTX Extension Period (Week 26 through Week 46)											Wk 48/ EOT/ET	30-Day Post-Treatment Follow-up Visit[25]	MTX Partner Pregnancy Follow-up
	Week (±3 d)													
	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	Wk 36	Wk 38	Wk 40	Wk 42	Wk 44	Wk 46		~30 days after last pegloticase infusion or MTX dose (±3 d)	~3 months after last MTX dose
Trial Procedure/ Assessment	**Inf: 14**	**Inf: 15**	**Inf: 16**	**Inf: 17**	**Inf: 18**	**Inf: 19**	**Inf: 20**	**Inf: 21**	**Inf: 22**	**Inf: 23**	**Inf: 24**			
Folic acid Rx filled[14]	Rx filled as needed													
Optional gout prophylaxis Rxs filled if needed[15]	Rxs filled as needed													
IR prophylaxis Rxs filled[16]	Rxs filled as needed													
MTX compliance/ reconciliation	X	X	X	X	X	X	X	X	X	X	X	X		
IR prophylaxis[16] and compliance (Yes/No)	X	X	X	X	X	X	X	X	X	X	X			
Folic acid compliance (Yes/No)	X	X	X	X	X	X	X	X	X	X	X	X		
Optional gout flare prophylaxis compliance (N/A, Yes/No)	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			
CCI [redacted]						X						X		
CCI [redacted]						X						X		
Pre-infusion CCI [redacted] sampling						X					X			
sUA[19]	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology						X						X		

	Optional Pegloticase + MTX Extension Period (Week 26 through Week 46)											Wk 48/ EOT/ET	30-Day Post-Treatment Follow-up Visit[25]	MTX Partner Pregnancy Follow-up
	Week (±3 d)													
	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	Wk 36	Wk 38	Wk 40	Wk 42	Wk 44	Wk 46		~30 days after last pegloticase infusion or MTX dose (±3 d)	~3 months after last MTX dose
Trial Procedure/ Assessment	**Inf: 14**	**Inf: 15**	**Inf: 16**	**Inf: 17**	**Inf: 18**	**Inf: 19**	**Inf: 20**	**Inf: 21**	**Inf: 22**	**Inf: 23**	**Inf: 24**			
Clinical chemistry						X						X		
eGFR (calculated by the central laboratory)						X						X		
Urine albumin: creatinine ratio						X						X		
hs-CRP						X						X		
Additional samples for future analysis[22]						X						X		
Pregnancy test[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	
CCI [redacted]						X						X		
Partner pregnancy[26]														X

AE = adverse event; d = day(s); DECT = dual-energy computed tomography; eGFR = estimated glomerular filtration rate; CCI [redacted] ET = early termination; EOT = End of Trial; G6PD = glucose-6-phosphate dehydrogenase; HAQ-DI = Health Assessment Questionnaire-Disability Index; hs-CRP = high-sensitivity C-reactive protein; Inf = infusion; IR = infusion reaction; IV = intravenous; MTX = methotrexate; N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug;
PK = pharmacokinetic; CCI [redacted]; Rx = prescription; SAE = serious adverse event; SC = subcutaneous; | CCI [redacted] sUA = serum uric acid; UA = uric acid; V= Visit; Wk(s) = Week(s).
NOTE: Unless stated otherwise, all procedures will be completed prior to pegloticase infusion.
* Week 24 is the final visit of the Pegloticase + MTX Treatment Period; trial drug is not administered for subjects who may not gain further benefit beyond 12 infusions based on the Principal Investigator's judgement.

Footnotes:
1. The Screening Visit can occur up to 42 days prior to the first dose of MTX at Week -6.

2. During the MTX Run-in Period, subjects with eGFR ≥45 mL/min/1.73 m^2 will inject SC MTX weekly at a starting dose of 15 mg at Weeks -6 and Week -5 increasing to 25 mg at Week -4 and continuing weekly throughout the trial. Subjects with eGFR ≥30 and <45 mL/min/1.73 m^2 will inject SC MTX at a starting dose of 10 mg at Week -6 and Week -5 increasing to 15 mg at Week -4 and continuing weekly throughout the trial; subjects unable to tolerate the 15 mg dose of MTX will be considered MTX Run-in Screen Failures. If a subject becomes unable to tolerate MTX at 25 mg doses, the folic acid dose may be increased from 1 to 2 mg/day and/or the MTX dosage may be decreased to 20 or 15 mg, but to no less than 15 mg. Subjects who are unable to tolerate MTX at a minimum dose of 15 mg during the Run-in Period regardless eGFR will be considered MTX Run-in Screen Failures.
3. Subjects will be enrolled at the Day 1 Visit to receive pegloticase 8 mg IV every 2 weeks from Day 1 through Week 22, inclusive. During this 24-week Pegloticase + MTX Treatment Period, subjects who meet the Individual Subject sUA Discontinuation Criteria or discontinue treatment for another reason will remain in the trial for biweekly visits, including the Week 24/End of Trial/ET and 30-Day Post-Treatment Follow-up Visits.
4. Prior to Week 22, subjects who end treatment due to sUA level or other reasons should complete the End of Pegloticase Visit within 2 weeks of the last infusion and continue with trial procedures without infusion. Subjects will also complete all regularly scheduled Follow-up Visits, including the 30-Day Post-Treatment Follow-up email/phone call and Week 24/End of Trial/ET Visits.
5. The Investigator or designee will collect a complete gout history, 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 screening visit, substance use history and all other medications up to the screening visit. Prior medications (not including gout medications and pegloticase) will be collected for 1 year prior to the screening visit. Detailed pegloticase use history, including reason for discontinuation and associated reactions, if any, will be collected.
7. A complete physical examination, including assessment of head, eyes, ears, nose and throat; heart; lungs; abdomen; skin; extremities; neurological status and musculoskeletal system, including an assessment for the presence of CCI as well as gout history and symptom severity, will be performed at the Screening Visit. A targeted physical examination per Investigator judgement will be conducted at all other indicated time points. On days when pegloticase is administered, the examination is conducted prior to pegloticase administration. At a minimum, the targeted physical examination should include assessment of heart, lungs and abdomen. Clinically significant findings from the targeted physical examinations will be recorded as AEs.
8. Routine vital signs, including blood pressure, respiratory rate, temperature and heart rate, will be measured. Heart rate and blood pressure measurements should be taken after the subject has been in a sitting position in a rested and calm state with proper positioning, including back support and feet flat on the floor, for at least 5 minutes. The subject's arm should be supported at heart level and the 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 trial visit. The Korotkoff phase V will be used to determine diastolic blood pressure. During the Pegloticase + MTX Treatment Period visits, vital signs 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. Height will be collected at the Screening Visit only.
9. Weight should be measured in kilograms or pounds when the subject is not wearing shoes. On days when pegloticase is administered, weight should be recorded prior to pegloticase administration.
10. Electrocardiogram should be completed during Screening and will be read at the site. When possible, a 12-lead electrocardiogram will also be performed at the time when a select AE of special interest (IR, anaphylaxis and major adverse cardiovascular event, defined as non-fatal stroke, non-fatal myocardial infarction, cardiovascular death and congestive heart failure) is suspected.
11. AEs/SAEs will be collected from the signing of the informed consent form until the 30-Day Post-Treatment Follow-up Visit. For each AE, the Investigator will be asked to record if the event was possibly an IR or anaphylaxis and if so, will be prompted to complete additional electronic case report forms. 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.
12. The initial DECT scan will be performed after the Screening Visit, during the MTX Run-in Period and prior to the Day 1 Visit. Subsequent DECT scans may be performed ±10 days from the scheduled visit date. Subjects who end pegloticase infusions prior to Week 24 should follow the scheduled time points and have a DECT scan at the End of Pegloticase (if applicable) and Week 24/End of Trial/ET Visits (detailed guidance is provided within the Imaging Manual). DECT will be carried out for all subjects where the site has the capability to conduct the test.
13. MTX will be dispensed and brought back to check compliance at each infusion visit. MTX should be injected 1 to 3 days prior to each pegloticase infusion; however, if a subject does not do so, MTX must be injected ≥60 minutes prior to each pegloticase infusion.

14. Subjects will take folic acid at a starting dose of 1 mg orally every day beginning Week -6 (preferably 2 days prior to the first dose of MTX) continuing until prior to the End of Pegloticase (if applicable) or until 1 week after the last pegloticase infusion for subjects who have not stopped pegloticase treatment. The folic acid dose can be increased or an alternative folate supplement can be used (see Section 9.4.6.3.2.2 for detailed instructions).
15. Before a subject begins the Pegloticase + MTX Treatment Period, he or she must have been taking at least 1 standard gout flare prophylaxis regimen (i.e., colchicine and/or NSAIDs and/or low-dose prednisone ≤10 mg/day) per protocol for ≥1 week before the first dose of pegloticase and continue flare prophylaxis for at least 6 months per American College of Rheumatology guidelines (FitzGerald et al, 2020). Gout flare prophylaxis from Week 26 to the end of the trial will be administered, if needed, at the discretion of the Principal Investigator.
16. IR prophylaxis includes fexofenadine (180 mg orally) and prednisone (50 mg orally) administered the night before each infusion; fexofenadine (180 mg orally), famotidine (20 mg orally), montelukast (10 mg orally) and acetaminophen (1000 mg orally) administered on the morning of each pegloticase infusion and methylprednisolone (125 mg IV) over an infusion duration between 10 and 30 minutes, prior to each pegloticase infusion.
17. CCI [redacted]
18. Serum samples for evaluation of CCI [redacted] will be collected prior to the first dose of MTX at Week -6, prior to pegloticase infusion on Day 1 and at Weeks 2, 6, 14, 22 and 36; and at the non-infusion End of Pegloticase (if applicable) or the Week 24 or 48/End of Trial/ET Visit. In the event of an AE suspected to be an IR, a serum sample will be collected at that time or at the subsequent visit for evaluation of pegloticase antibodies.
19. Serum samples for measurement of sUA levels will be collected at the Screening, Week -6 (prior to the first dose of MTX) and Week -2 Visits. On Day 1, a pre- and post-infusion sUA will be collected to be shipped to the central laboratory. For the remainder of trial visits beginning at Week 2 during the Pegloticase +MTX Treatment Period, 2 sUA samples will be collected within 48 hours PRIOR to each pegloticase infusion. One sample will be for sUA testing at the site's local laboratory and the second sample will be sent to the central laboratory (the central laboratory sample may be drawn separately from the local collection). Additional serum samples for sUA levels will be collected after the end of each pegloticase infusion prior to discharge at Weeks 10, 12, 14, 20, 22, 32, 34, 44 and 46. Single serum samples for measurement of sUA will also be collected at non-infusion visits at Weeks 21 and 23 and at the End of Pegloticase (if applicable) or the Week 24 or 48/End of Trial/ET Visit. Serum for sUA analysis will also be collected following the first 7 pegloticase infusions (Infusion 1, 2, 3, 4, 5, 6 and 7) at Day 1, Weeks 2, 4, 6, 8, 10 and 12, respectively. The sUA will be collected at the following non-infusion days: 1st (~24 hours), 4th (~96 hours), 7th (~168 hours) and 10th (~240 hours) day after each of the first 4 infusions, and 1st (~24 hours), and 7th (~168 hours) day after each infusion number 5, 6, 7. If infusion intervals of less than 2 weeks should occur due to scheduling issues the 1st day (~24hours) samples must be obtained at a minimum and also the 7th day (~168 hours) if feasible.
20.
21. G6PD testing should be performed by the central laboratory; however, if performed by the local laboratory, normal ranges should be provided.
22. Optional serum and urine samples will be collected from each consenting subject prior to the first dose of MTX at Week -6, prior to pegloticase infusion on Day 1 and at Weeks 14, 24, 36 and the End of Pegloticase (if applicable) and Week 24 or 48/End of Trial/ET Visits.
23. For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit. A urine pregnancy test will be performed at the End of Pegloticase (if applicable), Week 24 or 48/End of Trial/ET and 30 days after the last MTX dose if it is determined that the subject has not ovulated; a urine pregnancy test will be performed prior to MTX dosing during the MTX Run-in Period and prior to each pegloticase infusion at all other indicated visits.
24. CCI [redacted]
25. Thirty (30) days after the last MTX dose or pegloticase infusion (whichever is later), subjects will be contacted by telephone or email to review AEs, SAEs and concomitant medications. 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.
26. Male subjects who are non-vasectomized will be asked 3 months after MTX discontinuation regarding partner pregnancy.

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
ALT	alanine transaminase
AST	aspartate transaminase
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus disease 2019
DECT	dual-energy computed tomography
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
CCI	[redacted]
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
hs-CRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council for Harmonisation
CCI	CCI [redacted]
IND	Investigational New Drug
IR	infusion reaction
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous(ly)
MACE	major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
mPEG	methoxy PEG
MTX	methotrexate
NSAID	nonsteroidal anti-inflammatory drug
OL	open-label

Abbreviation	Definition
CCI	[redacted]
CCI	[redacted]
CCI [redacted]	[redacted]
SAE	serious adverse event
SC	subcutaneous
CCI [redacted]	CCI [redacted]
sUA	serum uric acid
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
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 trial documentation to be used in this trial 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, applicable trial 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 trial. A copy of the approved ICF will also be forwarded to the Sponsor or its designee. Appropriate reports on the progress of the trial 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 Trial

The Investigators will ensure that this trial 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 subject. The trial 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 trial after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.

The Investigator or designee must also explain that the subjects are completely free to refuse to enter the trial 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 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 trial by signing the revised ICF. Any revised ICF and written information must receive the IRB`s approval/favorable opinion before 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 trial 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 sign the revised ICF.

5.4 Compensation for Health Damage of Subjects/Insurance

The Sponsor maintains clinical trial insurance coverage for this trial in accordance with the laws and regulations of the country in which the trial 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's name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Trial findings stored in 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 trial 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 trial complies with the federal and/or regional legislation related to the privacy and protection of personal information (Health Insurance Portability and Accountability Act).

6 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

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

The trial will be conducted at approximately 10 to 15 trial sites in the United States. Prior to initiation of the trial, 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 trial and the 1-year period following its completion.

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

Table 6.1 Table of Non-Sponsor Trial Responsibilities

Trial Responsibility	Organization
Clinical drug supply and distribution	PCI Pharma Services
Central safety laboratory	LabCorp Central Laboratory Services
Clinical Research Organization	LabCorp Drug Development Inc.
External Adjudication Committee	WIRB-Copernicus Group Inc.
Central imaging vendor	BioClinica, Inc.

7 INTRODUCTION

7.1 Background

7.1.1 Gout

Gout affects approximately 4% of the United States population, is the most common form of inflammatory arthritis in men and is associated with decreased quality of life (Saag and Choi, 2006; Singh and Strand, 2008; Zhu et al, 2011; Sattui et al, 2014). The frequency of gout is increasing worldwide, with prevalence rates estimated to be as high as 7% in older men (Mikuls et al, 2005; Saag and Choi, 2006; Roddy and Doherty, 2010). While the exact prevalence is unknown, as many as 200,000 persons in the United States experience chronic symptoms of gout, despite trials of oral urate-lowering therapy. Uncontrolled 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) (Brook et al, 2010; Wertheimer et al, 2013; Khanna et al, 2016). These patients often have significant, disabling urate deposits in soft tissues and bone known as tophi.

7.1.2 Pegloticase

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

Two replicate pivotal Phase 3 trials for pegloticase were undertaken to establish the efficacy and safety of the product. The primary endpoint was defined as plasma uric acid (highly correlated to sUA) reduction to <6 mg/dL for 80% of the time in Months 3 and 6 combined. The pooled response rate for pegloticase 8 mg every 2 weeks was 42%, versus a placebo response rate of 0% (Sundy et al, 2011). There was also a greater reduction in complete resolution of ≥1 tophus in the every 2 weeks treatment group, and favorable effect of pegloticase treatment in the reduction of the number of tender and swollen joints. In subsequent open-label extension trials, pegloticase led to continued control of plasma uric acid, reduction in gout flares and continued resolution of tophi, suggesting continuing benefit with extended pegloticase treatment beyond the initial 6 months of therapy, particularly in subjects who met responder criteria in the placebo-controlled trials.

In the Phase 3 pivotal trials, deaths, SAEs, other adverse events (AEs), as well as the laboratory abnormalities were generally equally distributed across placebo and pegloticase treatment groups, with the clear exception of gout flares and infusion reactions (IRs). Pegloticase-treated subjects exhibited a higher rate of gout flares during Months 1-3 as uric acid was being acutely lowered, then a decrease in gout flares compared with placebo during Months 4-6. Despite use of prophylactic medications against hypersensitivity, including administration of corticosteroids, antihistamine and acetaminophen, in advance of each pegloticase infusion, IRs were seen in

22/85 (26%) of subjects receiving the 8 mg every 2 weeks regimen. There was no specified definition of anaphylaxis in the Phase 3 protocols and no investigator-reported events of anaphylaxis in the Phase 3 trials with pegloticase. However, in a post hoc review applying the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network criteria (Sampson et al, 2006), it was determined that across the Phase 2 and Phase 3 program, anaphylaxis occurred in 6.5% of subjects treated with pegloticase every 2 weeks. Anaphylaxis generally occurred within 2 hours after treatment. Manifestations included wheezing, peri-oral or lingual edema or hemodynamic instability, with or without rash or urticaria. All of these events had relatively rapid resolution with cessation of infusion.

In a post hoc analysis, the apparent role of immunogenicity in both loss of urate-lowering effect and incidence of IRs was appreciated. Only 2% of subjects with anti-pegloticase antibody titers exceeding 1:2430 maintained a urate-lowering response to pegloticase compared with 63% of subjects who were treated for at least 2 months without developing high-titer antibodies ($p<0.001$) (Sundy et al, 2011). The incidence of IRs was higher among subjects who developed high-titer antibodies compared with those who had titers that did not exceed 1:2430 (60% vs 19%; $p <0.001$) (Sundy et al, 2011). In addition, most IRs occurred when sUA levels were >6 mg/dL. Retrospective analyses showed that the loss of urate-lowering efficacy, as reflected by sUA of >6 mg/dL, preceded a subject's first IR, whenever it occurred, in 20 (91%) of 22 subjects treated with pegloticase every 2 weeks.

Reducing anti-drug antibodies with concomitant administration of the immunomodulatory agent methotrexate (MTX) has been shown to be useful with other infused products that lead to immunogenicity, such as adalimumab, in the setting of rheumatoid arthritis treatment (Burmester et al, 2015).

Because of the limited treatment options for patients with uncontrolled gout, immunomodulators have been co-administered with pegloticase in an effort to prevent anti-drug antibody formation and increase the length of effective pegloticase therapy, similar to what is done in other rheumatic diseases treated with biologics (Krieckaert et al, 2012; Lie et al, 2015). The successful use of immunomodulators (MTX, azathioprine, leflunomide and cyclosporine) with pegloticase in patients who receive pegloticase treatment for the first time is supported by case reports that examined different immunomodulatory agents with varying doses, schedules and routes given prior to the start of pegloticase (Hershfield et al, 2014; Berhanu et al, 2017; Freyne 2018; Albert et al, 2019; Botson and Peterson, 2019; Bessen et al, 2019a; Bessen et al, 2019b; Rainey et al, 2020; Masri et al, 2020). In case reports of MTX with pegloticase, the proportion of responders (based on each case's definition) was 100% (10/10 patients) (Botson and Peterson, 2019), 100% (7/7 patients) (Bessen et al, 2019a; Bessen et al, 2019b) and 80% (8/10 patients) (Albert et al, 2019); these responder rates are higher than the 42% rate observed in early Phase 3 clinical trials of pegloticase alone (Sundy et al, 2011). Similar to results of case studies, a recent prospective open-label clinical trial reported that a high proportion of subjects treated concomitantly with MTX (oral 15 mg/week started 4 weeks prior to the first pegloticase dose and throughout the pegloticase treatment period) maintained therapeutic response to pegloticase at 6 months (79% [11/14]) (Botson et al, 2020).

Given the promising clinical case series and prospective open-label trial with MTX in subjects who were treated with pegloticase for the first time, the current trial will prospectively examine whether pre-treatment and concomitant use of MTX with pegloticase can recapture the sUA response to pegloticase in subjects who were previously treated with pegloticase without a concomitant immunomodulator but did not maintain response.

7.1.2.1 CCI

7.1.2.2 Nonclinical 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.

7.1.2.3 Nonclinical Pharmacokinetics

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

7.1.2.4 Toxicology

The results from 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 trials (8 mg every 2 weeks) based on the area under the curve values from the 39-week, repeat-dose, dog study (high-dose).

An observation in the chronic toxicology studies is the finding of a dose-dependent increase in vacuolated cells. There were no associated clinical manifestations in any animals in which vacuolated cells were present. Evidence of vacuolated cells, especially in the spleen, has been observed with pegloticase administration in all the chronic toxicity studies as well as the embryo/fetal development and absorption, distribution, metabolism and excretion studies in the rat. It is thought that vacuolation of spleen macrophages is a result of lysosomal overloading following phagocytosis of persistent circulating macromolecules of high molecular weight. In the 39-week, long-term toxicity studies in dogs, vacuolated cells were also present in the basal area of the lamina propria within the duodenum and jejunum, adrenal cortical cells, hepatic Kupffer cells and the intimal cells within the aortic outflow area of the heart. The vacuolated cells in the

heart and adrenal gland did not stain as macrophages. In the aortic outflow tract of the heart, vacuoles were seen in the cytoplasm of endothelial cells in the intimal lining of the aorta. In the adrenal gland, vacuoles were located within cortical cells in the zona reticularis and zona fasciculata. The clinical significance of these findings and functional consequences are unknown.

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

7.1.2.5 Clinical Pharmacokinetics

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

Following single intravenous (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 (Trial M0403), pegloticase serum concentrations were not affected in a clinically meaningfully manner by 2 hemodialysis sessions. Pre- and post-dialyzer samples, as well as samples taken during dialysis, demonstrated that trial drug was not removed by the dialysis process.

No formal trials have been conducted to examine the effects of hepatic impairment on CCI .

7.1.2.6 Risks of Pegloticase

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 trial.

It is required that all subjects receive prophylactic treatment to reduce the risk of acute gout flares, unless medically contraindicated or not tolerated, as noted in the pegloticase prescribing information. Subjects will begin at least 1 protocol-specified standard gout flare prophylaxis regimen (i.e., colchicine and/or nonsteroidal anti-inflammatory drugs [NSAIDs] and/or low-dose prednisone ≤10 mg/day) for ≥1 week before the first dose of pegloticase and should continue flare prophylaxis for at least 6 months per American College of Rheumatology guidelines (FitzGerald et al, 2020).

Since IRs can occur, all subjects will receive pre-treatment prophylaxis consisting of antihistamine, acetaminophen, a leukotriene inhibitor and corticosteroids prior to each pegloticase infusion of pegloticase. To standardize this regimen, subjects will receive, at a minimum, fexofenadine (180 mg orally) and prednisone (50 mg orally) the night before each infusion, fexofenadine (180 mg orally), famotidine (20 mg orally), montelukast (10 mg orally) and acetaminophen (1000 mg orally) the morning of each pegloticase infusion and methylprednisolone (125 mg IV) given over an infusion duration between 10 and 30 minutes, prior to each pegloticase infusion.

The risk of anaphylaxis and IRs is higher in patients whose sUA level increases to >6 mg/dL. Monitoring 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 (Keenan et al, 2019).

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

7.1.3 Methotrexate Overview and Risks

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

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; and
- General: malaise, fatigue, dizziness, alopecia, photosensitivity.

Additionally, MTX can cause fetal death or teratogenic effects. If either partner is receiving MTX, pregnancy should be avoided during therapy and for a minimum of 3 months after MTX therapy for the non-vasectomized male. For females of childbearing potential, pregnancy should be avoided for at least 1 ovulatory cycle after MTX therapy.

Baseline assessment will include a complete blood count with differential, hepatic enzymes, renal function tests and a chest x-ray.

MTX is available in both oral and injection formulations; however, subcutaneous (SC) administration may overcome some limitations of oral MTX therapy. In a trial of the PK profiles of MTX following oral and SC administration, the bioavailability of MTX was greater at all dose levels tested (10 mg, 15 mg, 20 mg, and 25 mg) for SC compared with oral administration, and a

dose-proportional increase in PK parameters was noted across all doses (Schiff and Sadowski 2017).

In addition, various clinical experiences suggest that SC MTX is more effective than oral MTX and may provide significant benefit even in patients in whom oral MTX proved to be inadequate. The increased efficacy of SC MTX resulting from higher drug exposure compared with oral MTX has been associated with a similar safety profile as oral MTX and in some reports even a lower frequency of gastrointestinal complaints (Vena et al, 2018). In a 6-month prospective, randomized, double-blind controlled trial of oral and SC MTX administration in 384 patients with active rheumatoid arthritis, SC administration was significantly more effective than oral administration at the same MTX dosage, with no difference in tolerability (Braun et al, 2008).

This trial will use SC MTX to reduce and/or prevent the formation of anti-drug antibodies because subjects in this trial previously received pegloticase but did not maintain an sUA response, presumably due to anti-drug antibody formation.

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

7.2 Rationale for This Trial

Although pegloticase is highly effective, when administered without an immunomodulator, the formation of anti-drug antibodies results in a high non-responder rate. In Phase 3 trials in which pegloticase was administered without concomitant immunomodulation, 52% of subjects were non-responders, leaving many subjects with no alternative therapy options, since pegloticase is the last line of defense. Among patients who have previously failed pegloticase, there is an unmet need for treatment.

Retreatment with an immunomodulator following loss of efficacy of other biologics has been shown to regain efficacy. In inflammatory bowel disease patients with loss of response due to immunogenicity, the addition of immunomodulators to therapy resulted in undetectable anti-drug antibody levels and was an effective approach to recapture clinical response (Ben-Horin et al, 2013; Strik et al, 2017; Ungar et al, 2017).

Prophylactic use of immunosuppressive therapy, such as MTX with pegloticase may enable sustained treatment and improve outcomes. In case reports of 2 subjects, MTX was used as an adjunct to pegloticase treatment for refractory tophaceous gout. In 1 subject, high sUA levels developed prior to the third infusion. Adjunctive MTX treatment restored pegloticase response and the patient's sUA levels decreased and remained low for the remainder of treatment. Oral MTX was initiated at the first infusion in a second subject. Following a lapse in MTX compliance, low sUA levels achieved initially were increased. Re-initiation of MTX restored pegloticase response and the patient tolerated subsequent infusions (Bessen et al, 2019a).

Although there may be concerns for more severe IRs in this trial population upon retreatment with pegloticase due to relationship between anti-drug antibody development and IRs, analysis of IR severity among subjects treated with pegloticase every 2 weeks and who had more than

1 IR in the Phase 3 program showed that the majority (approximately 66%) had a second IR of the same or lower severity than the first IR.

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). An oral MTX dose of 15 mg is currently being studied in the randomized controlled trial to confirm if MTX can prevent anti-drug antibodies formation to increase responder rate and reduce risk of IR. In this trial, a higher SC dose of 25 mg (for subjects with estimated glomerular filtration rate [eGFR] ≥45 mL/min/1.73 m^2 [15 mg for subjects with eGFR ≥30 and <45 mL/min/1.73 m^2) will be used to increase the likelihood of success in those who previously failed pegloticase.

7.3 Rationale for Dose Selection

7.3.1 Pegloticase Dose Selection

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

7.3.2 Methotrexate Dose Selection

MTX is among the most well-studied agents shown to reduce anti-drug antibodies in numerous trials (Strand et al, 2017). MTX as monotherapy for rheumatoid arthritis and psoriatic arthritis is generally administered at doses of 7.5 to 15 mg/week, with doses titrated up as necessary and tolerated to 25 to 30 mg/week (Visser and van der Heijde, 2009; Ceponis and Kavanaugh, 2010; Mouterde et al, 2011; Mease 2013). These dose levels have generally been both effective and safe. A similar dose range of MTX has been used in combination with biologic disease-modifying antirheumatic drugs when the biologic disease-modifying antirheumatic drugs have been used as therapy for both rheumatoid and psoriatic arthritis, as well as other conditions (REMICADE Product Labeling, 2020; HUMIRA Product Labeling, 2018; CIMZIA Product Labeling, 2019). As discussed in Section 7.1.3, in the current trial, MTX will be administered SC, given its potential superior efficacy compared with oral administration.

A retrospective chart review of the effect of MTX and pegloticase in 10 uncontrolled gout patients provides support for the safety of the SC MTX with pegloticase regimen. Nine patients began SC MTX (25 mg weekly) prior to initiating pegloticase 8 mg every 2 weeks; the remaining patient began oral MTX (12.5 mg weekly) 14 days after the first pegloticase infusion. When MTX was administered with pegloticase, either as SC or oral formulation, the majority of patients (80%; 8/10) received at least 12 pegloticase infusions, were considered responders and no new safety concerns emerged (Albert et al, 2019).

The MTX dose in the current trial will be based on eGFR because renal excretion is the primary route of MTX elimination.

Bressolle et al. (1998) have shown that in rheumatoid arthritis patients, the half-life of MTX is doubled when creatinine clearance decreases to <45 mL/min. The RASUVO Full Prescribing Information indicates that the dose of MTX should be reduced in patients who have renal

impairment. The 2008 American College of Rheumatology recommendations for use of MTX (Saag et al, 2008) indicate that MTX is contraindicated when the estimated creatinine clearance is <30 mL/min. Based on this literature, only subjects with an eGFR ≥30 mL/min/1.73 m^2 will be eligible for enrollment. In this trial, a higher SC dose of 25 mg (for subjects with eGFR ≥45 mL/min/1.73 m^2 [15 mg for subjects with eGFR ≥30 and <45 mL/min/1.73 m^2) will be used to increase the likelihood of success in those who previously failed pegloticase.

8 TRIAL OBJECTIVES

The overall objective of this trial is to evaluate the efficacy and safety of pegloticase and MTX co-administered in subjects with uncontrolled gout who previously received pegloticase without a concomitant immunomodulator but did not maintain an sUA response (i.e., unable to maintain sUA <6 mg/dL while being treated with pegloticase alone and/or stopped pegloticase treatment due to an IR).

Primary Objective

The primary objective is to demonstrate that the response rate during Month 6 (Weeks 20, 21, 22, 23 and 24), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 6, is greater than 20% in subjects receiving pegloticase with MTX.

Secondary Objectives

To evaluate the effect of pegloticase with MTX on the following:

- 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.
- The proportion of subjects who experienced any of the following events from Day 1 to Week 24: IR leading to discontinuation of treatment, anaphylaxis or meeting Individual Subject sUA Discontinuation Criteria.
- The change from Baseline in urate deposition volume, measured by dual-energy computed tomography (DECT) scan.
- The change from Baseline in Health Assessment Questionnaire (HAQ) - Disability Index (HAQ-DI) score.
- The change from Baseline in HAQ pain score.
- The change from Baseline in HAQ health score.

Exploratory Objectives

To evaluate the effect of pegloticase with MTX on the following:

- 

Safety and Tolerability Objectives

To evaluate the effect of pegloticase with MTX on the following:

- The AE/SAE profile overall for pegloticase and MTX and the incidence of adverse events of special interest (AESIs), including IRs, anaphylaxis, gout flares and major adverse cardiovascular events (MACE, defined as non-fatal stroke, non-fatal myocardial infarction, cardiovascular death and congestive heart failure).
- The change from Baseline in safety laboratory test results, including high-sensitivity C-reactive protein (hs-CRP).
- The change from Baseline in vital signs.

9 INVESTIGATIONAL PLAN

9.1 Overall Trial Design and Plan

This is a Phase 4, multicenter, open-label trial of pegloticase with MTX in adult subjects with uncontrolled gout who were previously treated with pegloticase without a concomitant immunomodulator and stopped pegloticase due to failure to maintain sUA response and/or a clinically mild IR. Approximately 30 subjects will be enrolled. The treatment period with pegloticase + MTX will be approximately 24 weeks, with optional extension up to 48 weeks.

The trial design will include 5 distinct components:

1) a Screening Period, lasting up to 42 days;
2) a 6-week MTX Tolerability Assessment Period (hereafter referred to as the MTX Run-in Period);
3) a 24-week Pegloticase + MTX Treatment Period, which will include a Week 24/End of Trial/Early Termination Visit (subjects that end MTX and pegloticase treatment prior to the Week 24 will remain on trial for follow up until the Week 24 visit);
4) an Optional Pegloticase + MTX Extension Period from Week 24 to Week 48, if a subject may gain further benefit with additional pegloticase treatment per the discretion of the Principal Investigator, which will include a Week 48/Optional End of Trial/Optional Early Termination Visit and
5) a 30-Day Post-Treatment Follow-up (Phone/Email) 30 days after the last pegloticase infusion or last dose of MTX (for subjects who are unable to tolerate MTX during the MTX Run-in Period and do not dose pegloticase). Subjects that end MTX and pegloticase treatment prior to Week 24 and remain on trial for at least 30 days prior to Week 24 will complete the 30-Day Post-Treatment Follow-Up as part of the visits following the End of Pegloticase visit.

All subjects who meet eligibility criteria at Screening will begin titrating up to a once weekly SC MTX at a target dose of 25 mg (if eGFR is ≥45 mL/min/1.73 m^2) or 15 mg (if eGFR is ≥30 and <45 mL/min/1.73 m^2) for 6 weeks prior to the first dose of pegloticase. Subjects will also take folic acid at a starting dose of 1 mg orally every day beginning at Week -6 (preferably 2 days prior to the first dose of MTX) continuing until prior to the End of Pegloticase Visit (if applicable) or until 1 week after the last pegloticase infusion for subjects who have not stopped pegloticase treatment. A higher folic acid dose or an alternative folate supplement will be allowed (see Section 9.4.1.3 for specific instructions).

Subjects must be able to tolerate MTX at a minimum dose of 15 mg during the 6-week MTX Run-in Period to be eligible to participate in the Pegloticase + MTX Treatment Period, regardless of Baseline eGFR. Subjects who are unable to tolerate MTX 15 mg during the MTX Run-in Period will be considered MTX Run-in Screen Failures.

Female subjects of childbearing potential who inject at least 1 dose of MTX will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of MTX to verify that at least 1 ovulatory cycle has occurred since the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. For those subjects who inject at least 1 dose of MTX and who are non-vasectomized males, an inquiry will be made 3 months after the subject's last dose of MTX regarding partner pregnancy.

All subjects who meet the inclusion/exclusion criteria and complete the MTX Run-in Period will be considered enrolled subjects and will receive the first pegloticase infusion on Day 1. All subsequent doses and trial visits will be scheduled based on the Day 1 Visit date.

Prior to the Pegloticase + MTX Treatment Period, subjects will begin taking at least 1 standard gout flare prophylaxis regimen (i.e., colchicine and/or NSAIDs and/or low-dose prednisone ≤10 mg/day) per protocol beginning ≥1 week before the first dose of pegloticase, continuing for at least 6 months per American College of Rheumatology guidelines (FitzGerald et al, 2020). For IR prophylaxis, fexofenadine (180 mg orally) and prednisone (50 mg orally) will be taken the night before each pegloticase infusion; fexofenadine (180 mg orally), famotidine (20 mg orally), montelukast (10 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each pegloticase infusion; methylprednisolone (125 mg IV), over an infusion duration between 10 and 30 minutes, will be administered prior to each pegloticase infusion.

During the Pegloticase + MTX Treatment Period, pegloticase 8 mg will be administered IV every 2 weeks from Day 1 through the Week 22/Week 46, after all predose trial visit assessments have been completed at each visit. The date, start and stop time of infusion will be recorded.

During the Pegloticase + MTX Treatment Period, subjects will be instructed to inject MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase infusion (on the weeks when pegloticase is administered); however, if a subject does not do so, MTX must be injected ≥60 minutes prior to each pegloticase infusion. One additional weekly dose of MTX will be injected after the last pegloticase infusion for subjects who have not stopped pegloticase due to individual subject sUA discontinuation criteria. If the subject discontinues pegloticase due to the stopping rule or other reason, MTX and folic acid should also be discontinued.

After Day 1, if a subject becomes unable to tolerate MTX, the folic acid dose can be increased, an alternative folate supplement may be used and/or the MTX dosage may be reduced or discontinued based on pre-defined criteria (see Section 9.4.6.3.2.2 for detailed instructions) and the subject may remain in the trial and continue pegloticase infusions. Every attempt should be made to re-start the MTX in subjects once their MTX-associated symptoms have improved or their laboratory tests have normalized.

The Investigator will review the subject clinical status and CCI (Appendix 17.8) at Week -6; prior to pegloticase infusion at the Week 24 and Week 36 Visits (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period); and at the End of Pegloticase (if applicable) and Week 24 or 48/End of Trial/Early Termination Visits.

After the Week 24 or 48 Visit (or End of Pegloticase Visit [if applicable]) or upon pegloticase discontinuation, subjects should resume regular care for gout per the judgment of the treating physician, including resumption of urate-lowering therapy, if appropriate.

Two sequential cohorts of subjects will be enrolled in this trial. Cohort 1 is targeted to enroll 10 subjects who previously failed to maintain sUA response with pegloticase monotherapy and stopped pegloticase treatment without a history of pegloticase-related IR. After 7 and 10 subjects in Cohort 1 complete at least 6 infusion visits, safety assessments of IR and anaphylaxis from available subjects' data will be performed by the Safety Review Team (comprising members of the Horizon Clinical Development and Patient Safety and Pharmacovigilance Teams) based on pre-determined tolerability criteria. If a subject discontinues treatment or discontinues the trial prior to the 6th infusion, their available data will be included in the safety assessment. If the safety assessment during Cohort 1 indicates that the pegloticase infusions are well tolerated based on the pre-determined criteria (see tolerability criteria), then the trial can begin enrolling Cohort 2. If the safety assessment indicates that the pegloticase infusions are not well tolerated based on the pre-determined tolerability criteria, then the trial will cease to screen and enroll new subjects. Subjects who are ongoing and benefitting from continued treatment, as determined by the Principal Investigator at the time of the termination of new subject screenings, will be permitted to continue treatment and trial visits.

The aim is to enroll up to 20 subjects in Cohort 2; subjects who failed to maintain sUA response with pegloticase monotherapy and or experienced a pegloticase related clinically mild IR . After 3, 6, 10, 15 and 20 subjects in Cohort 2 complete 6 infusion visits, safety assessments of IR and anaphylaxis from available subjects' data will be performed by the Safety Review Team. If the safety assessment indicates that the pegloticase infusions are not well tolerated based on the pre-determined tolerability criteria (see tolerability criteria) or in the absence of subjects with a history of pegloticase-related clinically mild IR, the trial will continue enrolling subjects without a history of pegloticase-related clinically mild IR to reach a total of 30 subjects enrolled for the trial.

Depending on any potential safety signals reported (e.g., serious IR or any SAE related to pegloticase infusion), regular quarterly and/or ad hoc safety assessments will be conducted during the trial as specified in the Safety Management Plan and the Safety Review Team Charter. The regular quarterly reviews will include review of the database by the Safety Review Team and will be conducted as set out in the Safety Management Plan. The first safety review meeting will occur approximately after the first 3 subjects in Cohort 1 complete at least 12 weeks of the Pegloticase + MTX Treatment period (6 infusion visits). The Safety Review Team could stop the trial for other significant safety reasons.

If 3 events of anaphylaxis (as assessed by PI) occur, an Adjudication Committee (composed of independent experts external to Horizon) (Section 9.5.6) will be established for this trial to adjudicate the AESIs of Anaphylaxis at a frequency defined in the Adjudication Committee Charter. The AESI of IR, MACE and gout flare will not be adjudicated.

Samples for measurement of sUA levels will be collected at Screening, during the MTX Run-in Period, pre- each infusion, post-infusion on Day 1 and at the Week 10, 12, 14, 20, 22, 32, 34, 44 and 46 Visits and on non-infusion visits on the 1st (~24 hours), 4th (~96 hours), 7th (~168 hours) and 10th (~240 hours) day after the first 4 infusions (Infusions 1, 2, 3, 4) and on the 1st (~24 hours) and the 7th (~168 hours) day after the 5th , 6th and 7th infusion; (i.e., Day 1 through prior to Week 14), Weeks 21 and 23, and at the End of Pegloticase (if applicable) or the Week 24 or 48/End of Trial/Early Termination Visit.

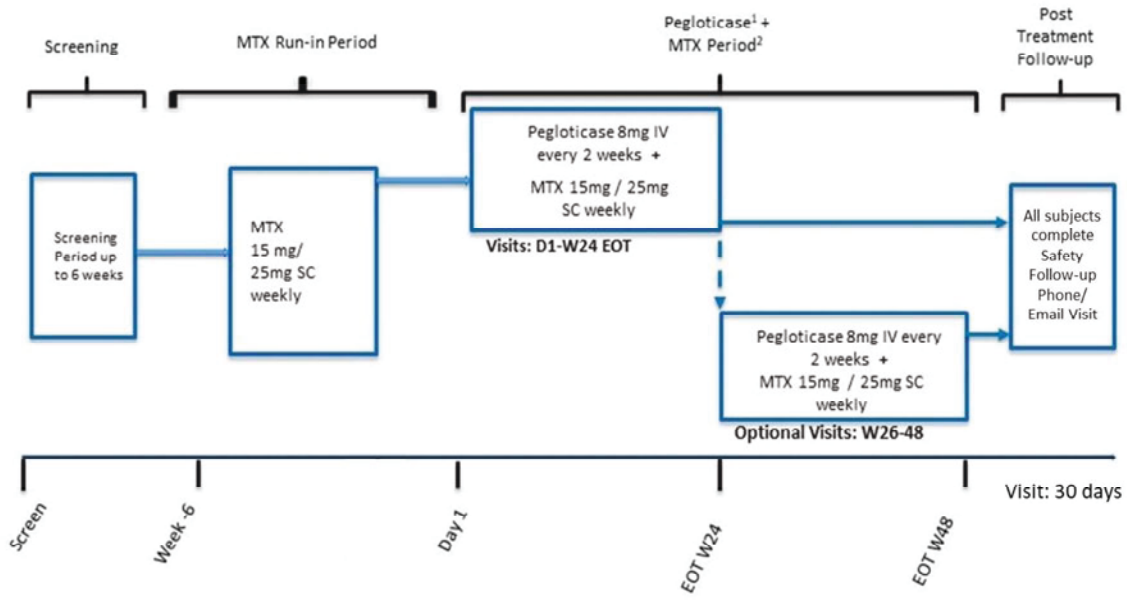
Samples will be collected for CCI [redacted] and CCI [redacted] as indicated in Section 2.1 (Schedule of Assessments).

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 and urine test, will be performed.

The total blood volume to be collected from each subject during this trial is approximately 450 mL.

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

Figure 9.1 Schematic of Trial Design



D = Day; EOT = End of Trial; IV = intravenous; MTX = methotrexate; SC = subcutaneous; sUA = serum uric acid; W = Week

1 Individual subjects who meet the sUA discontinuation criteria will end pegloticase therapy, complete the End of Trial procedures and remain in the trial.

2 Key efficacy and safety assessments will be conducted during Weeks 10, 12, 14, 20, 21, 22, 23 and 24.

9.2 Discussion of Trial Design

This is a Phase 4, multicenter, open-label, efficacy and safety trial of pegloticase in combination with SC MTX in adult subjects with uncontrolled gout, who previously received pegloticase without a concomitant immunomodulator and stopped pegloticase due to a clinically mild pegloticase-related IR and/or failure to maintain sUA response.

Immunogenicity (anti-pegloticase antibodies) in response to pegloticase therapy can lead to loss of therapeutic response and/or AEs, including IRs. For patients who previously lost therapeutic response to pegloticase treatment without a co-concomitant immunomodulator due to immunogenicity, a potential strategy to regain therapeutic efficacy with pegloticase is pretreatment followed by co-administration of immune-modulating therapy. MTX is the most commonly used non-biological disease-modifying agent worldwide and is frequently used in combination with other biological therapies (Strand et al, 2017), and has been shown to recapture clinical response of other biologic treatment after initial therapeutic efficacy is lost due to immunogenicity (Ben-Horin et al, 2013; Strik et al, 2017; Ungar et al, 2017). In the current trial, MTX given SC will be used as an immunomodulator co-administered with pegloticase to subjects who previously failed pegloticase alone.

This trial will include up to a 6-week Screening Period, a 6-week MTX Run-in Period, a 24-week Pegloticase + MTX Period, an Optional Pegloticase + MTX Extension Period from Week 24 to Week 48, if a subject may gain further benefit with additional pegloticase treatment per the discretion of the Principal Investigator and a Post-Treatment Follow-up Period.

The Safety Review Team (Section 9.5.5) will assess the tolerability of pegloticase using the tolerability criteria (see Section 9.5.4.1.1.5).

9.3 Selection of Trial Population

9.3.1 Inclusion Criteria

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

1. Willing and able to give informed consent.
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.
3. Adult men or women ≥18 years of age.
4. Uncontrolled gout, defined by the following criteria:
    - Hyperuricemia during the Screening Period, defined as sUA ≥6 mg/dL, and;
    - Failure to maintain normalization of sUA with xanthine oxidase inhibitors at the maximum medically appropriate dose or with a contraindication to xanthine oxidase inhibitor therapy based on medical record review or subject interview, and;
    - Symptoms of gout, including at least 1 of the following:
        - Presence of at least 1 tophus
        - Recurrent flares, defined as 2 or more flares in the 12 months prior to Screening
        - Presence of chronic gouty arthritis

5. Subject was previously treated with pegloticase without concomitant immunomodulation and stopped pegloticase due to failure to maintain sUA reduction response (had ≥1 sUA >6 mg/dL within 2 weeks post pegloticase infusion) and did not experience an IR (Cohort 1) and/or stopped pegloticase treatment due to pegloticase-related clinically mild IR (Cohort 2) (see guidance on assessment of IR symptoms and severity in Appendix 17.9). A Sponsor Adjudication Committee will review the signs, symptoms and treatment administered for the prior IR associated with pegloticase infusion before subjects with history of mild IR are enrolled.
6. Subject for whom the last pegloticase infusion occurred >6 months prior to Screening.
7. Willing to discontinue any oral urate-lowering therapy for at least 7 days prior to Day 1 and remain off other urate-lowering therapy during the Pegloticase + MTX Treatment Period.
8. 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 pregnancy tests during Screening.
    - Subjects must agree to use 2 reliable forms of contraception during the trial, 1 of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started ≥1 full cycle prior to Week -6 (start of MTX) and continue for 30 days after the last dose of pegloticase, or at least 1 ovulatory cycle after the last dose of MTX (whichever is the longer duration after the last dose of pegloticase). 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.
9. Men who are not vasectomized must agree to use appropriate contraception so as to not impregnate a female partner of reproductive potential during the trial, beginning with the initiation of MTX at Week -6 and continuing for at least 3 months after the last dose of MTX.
10. Able to tolerate MTX at SC doses of at least 15 mg during the MTX Run-in Period, regardless of eGFR status.

9.3.2 Exclusion Criteria

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

1. Known history of medically confirmed prior anaphylactic reaction.
2. Known history of moderate or severe IR (including but not limited to difficulty in breathing, hypotension, generalized urticaria, generalized erythema, angioedema and/or required treatment with IV steroids or epinephrine; see guidance on assessment of anaphylaxis/IR symptoms and severity in Appendix 17.9) or other SAEs related to pegloticase or any other pegylated product treatment.
3. Weight >160 kg (352 pounds) at Screening.

4. Any serious acute bacterial infection, unless treated and completely resolved with antibiotics at least 2 weeks prior to the Week -6 Visit.
5. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis.
6. Current or chronic treatment with systemic immunosuppressive agents, such as MTX, azathioprine, cyclosporine, leflunomide, cyclophosphamide or mycophenolate mofetil.
7. Current treatment with prednisone >10 mg/day or equivalent dose of another corticosteroid on a chronic basis (defined as 3 months or longer).
8. Known history of any solid organ transplant surgery requiring maintenance immunosuppressive therapy.
9. Known history of hepatitis B virus surface antigen positivity or hepatitis B DNA positivity, unless treated, viral load is negative and no chronic or active infection confirmed by hepatitis B virus serology.
10. Known history of hepatitis C virus RNA positivity, unless treated and viral load is negative.
11. Known history of human immunodeficiency virus positivity.
12. G6PD deficiency (tested at the Screening Visit).
13. Severe chronic renal impairment (eGFR <30 mL/min/1.73 m^2) at the Screening Visit based on 4 variable Modification of Diet in Renal Disease [MDRD] formula or currently on dialysis.
14. Non-compensated congestive heart failure, hospitalization for congestive heart failure or treatment for acute coronary syndrome (myocardial infarction or unstable angina) within 3 months of the Screening Visit, current uncontrolled arrhythmia or current uncontrolled blood pressure (>160/100 mmHg) prior to Week -6.
15. 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.
16. Prior treatment with another recombinant uricase (rasburicase) or concomitant therapy with a PEG-conjugated drug (see Appendix 17.10 for a list of PEG-conjugated drugs).
17. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product.
18. Contraindication to MTX treatment or MTX treatment considered inappropriate.
19. Known intolerance to MTX.
20. Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to MTX administration at Week -6 or plan to take an investigational drug during the trial.
21. Current liver disease, as determined by alanine transaminase (ALT) or aspartate transaminase (AST) >1.25 × upper limit of normal (ULN) or albumin <lower limit of normal at the Screening Visit.
22. Currently receiving systemic or radiologic treatment for ongoing cancer, excluding non-melanoma skin cancer.

23. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix.
24. White blood cell count $<4.0 \times 10^9$/L, hematocrit <32% or platelet count $<75 \times 10^9$/L.
25. Diagnosis of osteomyelitis.
26. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
27. Unsuitable candidate for the trial (e.g., cognitive impairment), based on the opinion of the Investigator, 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 trial.
28. Alcohol use in excess of 3 alcoholic beverages per week.
29. A known intolerance to all protocol standard gout flare prophylaxis regimen (i.e., unable to tolerate any of the following 3 agents: colchicine, NSAIDs or low- dose prednisone ≤10 mg/day).
30. Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest x-ray may be performed during Screening.

9.3.3 Removal of Subjects From Therapy or Trial

All subjects are free to withdraw from trial 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 trial at any time. However, subjects who are removed from pegloticase therapy should remain in the trial unless they withdraw consent.

9.3.3.1 Removal of Subjects From Pegloticase Therapy

For subjects who do not complete therapy through Week 24 or 48, the reason for discontinuation from pegloticase therapy 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.
- Lack of Efficacy.
- AE. 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.
- Physician Decision. The Investigator has determined that pegloticase administration poses an unacceptable risk to the subject (specify reason).
- Withdrawal by Subject. Subject refusal of additional therapy (specify reason).
- Trial Terminated by Sponsor. The Sponsor, IRB or regulatory agency terminates the trial.
- Pregnancy.
- Death.

9.3.3.1.1 Trial Considerations for Subjects Ending Pegloticase Infusions Prior to Week 24 or Week 48

- MTX, along with folic acid, will be discontinued at the time of cessation of pegloticase infusions prior to Week 24 or 48.
- All subjects will complete the End of Pegloticase Visit and will remain in the trial through Week 24 (if End of Pegloticase Visit occurred before Week 24) 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, including the 30-Day Post-Treatment Follow-up and Week 24/End of Trial/Early Termination Visits, but are especially encouraged to complete trial visits at the trial site for key efficacy and safety assessments at Weeks 10, 12, 14, 20, 21, 22, 23 and 24, so that sUA laboratory and other key assessments can be completed. During visits between these key efficacy and safety collection visits, in subjects who have stopped infusions, subjects may complete trial visits in person or via telephone to collect AE, concomitant medication 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;
    - IR prophylaxis;
    - IR prophylaxis compliance;
    - Folic acid compliance;
    - Pegloticase infusion;
    - CCI ;
    - Pre-infusion CCI sampling; and
    - MTX drug/dispensation related items.
- Re-introduction of oral urate-lowering therapies should not start until after the Week 24 or 48/End of Trial/Early Termination Visit (or End of Pegloticase Visit [if applicable] laboratory tests are collected.

If a subject discontinues treatment or discontinues the trial prior to the 6th infusion, their available data will be included in the safety assessment conducted by the Safety Review Team.

Subjects who elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period will complete the 30-Day Post-Treatment Follow-up after the final pegloticase infusion but are not required to return for biweekly visits.

9.3.3.2 Removal of Subjects From Trial

For subjects who discontinue from the trial prior to Week 24 or 48, the reason for discontinuation from the trial 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 Subject. The subject withdraws from the trial. 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.
- Trial Terminated by Sponsor. The Sponsor, IRB or regulatory agency terminates the trial.
- Death.

9.3.4 Replacement Policy

9.3.4.1 Subjects

In general, subjects who prematurely discontinue from the trial for any reason will not be replaced. An exception may be made for subjects who are unevaluable due to the impact of the coronavirus disease 2019 (COVID-19) pandemic and associated restrictions on movement and work. Subjects unable to receive treatment or be evaluated due to restrictions during the COVID-19 pandemic may be replaced, at the discretion of the Sponsor. This may result in more subjects than originally planned being enrolled into the trial to allow for the originally planned number to be evaluable for the primary efficacy analysis.

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 a SC dose of at least 15 mg weekly during the MTX Run-in Period will be considered MTX Run-in Screen Failures.

Subjects who fail screening or are an MTX Run-in Screen Failure may be allowed to rescreen, or retest laboratories for the trial if both the Investigator and Sponsor are in agreement regarding rescreening/retesting and if the Investigator determines that the subject can satisfy all of the eligibility criteria.

9.4 Treatments

9.4.1 Treatments Administered

9.4.1.1 Methotrexate

During the MTX Run-in Period, which begins 6 weeks prior to the first dose of pegloticase, subjects with eGFR ≥45 mL/min/1.73 m^2 will inject SC MTX weekly at a starting dose of 15 mg

at Weeks -6 and Week -5 increasing to 25 mg at Week -4 and continuing weekly throughout the trial. Subjects with eGFR ≥30 and <45 mL/min/1.73 m^2 will inject SC MTX weekly at a starting dose of 10 mg at Week -6 and Week -5 increasing to 15 mg at Week -4 and continuing weekly throughout the trial. If a subject becomes unable to tolerate MTX at 25 mg doses, the folic acid dose may be increased from 1 to 2 mg/day and/or the MTX dosage may be decreased to 20 or 15 mg, but to no less than 15 mg. Subjects who cannot tolerate MTX at a minimum dose of 15 mg during the MTX Run-in Period will be considered MTX Run-in Screen Failures, regardless of their Baseline eGFR.

During the MTX Run-in Period, if a dose is missed, it should be injected 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. If a subject misses more than 2 doses of MTX during the 6-week Run-in Period, the Principal Investigator should contact the Sponsor to discuss eligibility of the subject for enrollment in the Pegloticase + MTX Treatment Period.

During the Pegloticase + MTX Treatment Period, subjects will be instructed to inject MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase infusion (on the weeks when pegloticase is administered); however, if a subject does not do so, MTX must be injected ≥60 minutes prior to each pegloticase infusion. One additional weekly dose of MTX will be injected after the last pegloticase infusion for subjects who have not stopped pegloticase due to individual subject sUA discontinuation criteria. If the subject discontinues pegloticase due to the stopping rule or other reason, MTX should also be discontinued.

After Day 1, if a subject becomes unable to tolerate MTX, the folic acid dose can be increased, an alternative folate supplement may be used and/or the MTX dosage may be reduced or discontinued based on pre-defined criteria and the subject may remain in the trial and continue pegloticase infusions (see Section 9.4.6.3.2.2 for detailed instructions). Every attempt should be made to re-start the MTX in subjects once their MTX-associated symptoms have improved or their laboratory tests have normalized.

MTX for SC injection in auto-injectors (7.5, 10, 15, 20, 25 mg) will be provided to all subjects (RASUVO Full Prescribing Information). For each subject, the MTX dose will be based on their Baseline eGFR value.

Refer to Section 9.4.12 for contraception requirements.

9.4.1.2 Pegloticase

All subjects who meet the entry criteria and tolerate SC MTX at a minimum dose of 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 12 infusions from Day 1 through Week 22, inclusive (Pegloticase + MTX Treatment Period) or a total of 24 infusions from Day 1 through Week 46, inclusive (Pegloticase + MTX Treatment Period and Optional Pegloticase + MTX Extension Period), for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement. 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. On Day 1, pre- and post-infusion sUA results must be reported by the central laboratory. For the remainder of the trial beginning at Week 2, 2 sUA samples will be collected within 48 hours PRIOR to pegloticase infusion and results reported by the local laboratory and central laboratory (see Section 9.5.1.1).

After the Week 24 or 48 Visit (or End of Pegloticase Visit [if applicable]) or upon pegloticase discontinuation, subjects should resume regular care for gout per the judgment of the treating physician, including resumption of urate-lowering therapy, if appropriate.

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, generally over 120 minutes. Pegloticase will not be administered as an IV push or bolus.

If 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 and time of the start and stop time of the flush will be recorded.

9.4.1.3 Folic Acid

Subjects will also take folic acid at a starting dose of 1 mg orally every day beginning at Week -6 (preferably 2 days prior to the first dose of MTX) until prior to the End of Pegloticase Visit (if applicable) or until 1 week after the last pegloticase infusion for subjects who have not stopped pegloticase treatment.

During the MTX Run-in Period, if minor clinical symptoms emerge, such as mild stomatitis, mild gastrointestinal discomfort or fatigue, the Investigator may increase the folic acid dose from 1 mg/day to 2 mg/day.

During the Pegloticase + MTX Treatment Period after Day 1, if MTX toxicity-related laboratory findings or symptoms (such as nausea, fatigue) occur, the Investigator may increase the folic acid dose from 1 mg/day to 2 mg/day. If after more than 1 week of taking 2 mg/day folic acid, the sign/symptom or laboratory abnormalities do not resolve or improve, the subject is allowed to switch to oral leucovorin at 10 mg/week, given 10 to 24 hours POST each MTX injection, at the discretion of the Investigator. In this case, the Investigator should discuss the timing of oral leucovorin administration relative to the MTX injection with the Medical Monitor to ensure subject compliance. Leucovorin taken before, at the time of or too soon (<8 hours) after MTX injection will likely reduce the efficacy of MTX.

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

Prescriptions are to be filled at a local pharmacy, as needed. At trial visits, the subject will be asked whether folic acid was taken per protocol.

9.4.1.4 Gout Flare Prophylaxis

All subjects will receive standardized prophylactic treatment to reduce the risk of acute gout flares, beginning ≥1 week before the first dose of pegloticase, continuing for at least 6 months per American College of Rheumatology guidelines (FitzGerald et al, 2020). Before a subject begins the Pegloticase + MTX Treatment Period, he or she must have been taking at least 1 standard gout flare prophylaxis regimen (i.e., colchicine and/or NSAIDs and/or low-dose prednisone ≤10 mg/day) per protocol. Gout flare prophylaxis is optional from Week 26 to the end of the trial if needed at the discretion of the Principal Investigator.

Prescriptions are to be filled at a local pharmacy, as needed. At trial visits, the subject will be asked whether gout flare prophylaxis was taken per protocol.

9.4.1.5 Infusion Reaction Prophylaxis

Since IRs can occur with pegloticase, all subjects will receive IR prophylaxis prior to each pegloticase infusion, consisting of antihistamines, acetaminophen, a leukotriene inhibitor and corticosteroids. To standardize this regimen, fexofenadine (180 mg orally) and prednisone (50 mg orally) will be taken the night before each pegloticase infusion. Fexofenadine (180 mg orally), famotidine (20 mg orally), montelukast (10 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each pegloticase infusion. Methylprednisolone (125 mg IV), given over an infusion duration between 10 and 30 minutes prior to each pegloticase infusion will be administered.

Substitution of the corticosteroid is generally 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. IR medications administered prior to each pegloticase infusion will be supplied by the site.

Prescriptions are to be filled at a local pharmacy, as needed. At trial visits, the subject will be asked 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 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 mPEG. Excipients include disodium hydrogen phosphate dihydrate, sodium chloride, sodium dihydrogen phosphate dihydrate and water for injection.

9.4.2.2 Methotrexate

MTX for SC injection in auto-injectors (7.5, 10, 15, 20, 25 mg) will be provided to all subjects. For each subject, the MTX dose will be based on their Baseline eGFR value.

See RASUVO Full Prescribing Information for additional detail.

9.4.3 Labeling

Pegloticase (KRYSTEXXA®) and MTX will be supplied by PCI Pharma Services.

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. An ancillary label will be fixed to the vial and carton that identifies the trial, 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 in auto-injectors. An ancillary label will be fixed to the auto-injector and carton that identifies the trial, allows subject information to be entered and contains the investigational use caution statement according to the FDA Title 21 CFR Part 312 requirements. Each auto-injector and carton label will have a unique number. Auto-injectors will be provided to trial subjects at the Week -6 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° and 25°C (68° and 77°F), protected from light and will not be frozen; excursions to 15° to 30°C (59° to 86°F) will be permitted.

9.4.5 Drug Accountability

Clinical supplies will be dispensed only in accordance with this protocol. Accurate records of the clinical supplies received, the amount dispensed for each subject and the amount remaining at the conclusion of the trial will be maintained. Each trial site will also maintain individual subject drug logs/electronic logs to account for MTX auto-injectors and subject compliance will be monitored by the site at each visit (see Section 9.4.11).

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

The Trial Pharmacy Manual contains more detailed information on MTX and pegloticase packaging, labeling, storage and destruction.

9.4.6 Trial Drug Administration and Timing of Dose for Each Subject

9.4.6.1 Description of Clinical Supplies

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

9.4.6.2 Determination of Dose Volume

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

In the event of any potential safety signals reported (e.g., serious IR or any SAE related to pegloticase infusion), additional IR mitigation approaches, such as a slower pegloticase infusion rate, can be implemented. 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

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 particulate matter or discoloration 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 infusion must be started within 4 hours of dilution. Before administration, the diluted solution of pegloticase should be allowed to reach room temperature. Pegloticase must never be subjected to artificial heating.

9.4.6.3.2 Dose Modifications, Interruptions and Delays

9.4.6.3.2.1 Pegloticase Modifications

In the event of potential IR safety signals identified during the pegloticase infusion, or when the pre-infusion sUA level is >6mg/dL, additional IR mitigation approaches, such as a slower pegloticase infusion rate, can be implemented.

Infusion of pegloticase will be immediately held if the subject experiences any significant IR such as respiratory distress, agitation, chest or back pain, urticaria or another clinically significant event occurring during infusion. If the AE meets the definition of an SAE for IR, the infusion should not be restarted unless the site Investigator determines it is safe to do so. 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 at a slower infusion rate. An example of an ~150-minute infusion procedure in 250 mL volume (relative to the standard steady rate over 120 minutes) that can be implemented at the discretion of the Investigator is presented in Table 9.1.

Table 9.1 Sample Pegloticase Infusion Rate Modification Following an Infusion Reaction

Time Interval	Staggered Rate (Over ~150 Minutes)	Standard Steady Rate (Over 120 Minutes)
First 30 minutes	1.0 mL/min (30 mLs)	2.08 mL/min
Second 30 minutes	1.5 mL/min (45 mLs)	2.08 mL/min
Third 30 minutes	2.0 mL/ min (60 mLs)	2.08 mL/min
Fourth 30 minutes	2.0 mL/min (60 mLs)	2.08 mL/min
Last 27.5 minutes	2.0 mL/min (55 mLs)	Done

Alternatively, a larger volume of diluent, not to exceed 500 mL can be used. In this case, the infusion duration will be extended to a minimum of 3 hours. The total volume and duration of infusion will be captured in the medical record and eCRF.

Infusion of pegloticase may be held or delayed if the subject has an ongoing SAE or AE/SAE that occurs prior to the infusion. The status of subjects with skipped infusions will be discussed with the Investigator and the Sponsor's Medical Monitor on a case-by-case basis to determine whether the subject should continue to the next scheduled infusion or proceed to the End of Pegloticase Visit.

If a confirmed anaphylaxis event occurs in any subject, further dosing with pegloticase for that subject will be discontinued.

9.4.6.3.2.2 MTX Dose Titration Algorithm and Intolerance Criteria

During the MTX Run-in Period, a subject will be considered an MTX Run-in Screen Failure if any of the following new laboratory findings (repeat laboratory tests may be needed to confirm the findings) or symptoms reflecting MTX intolerance occur:

1. Abnormal hematology findings:
    a. White blood cell count $<3.5 \times 10^9$/L;
    b. Platelet count $<75 \times 10^9$/L; and
    c. Hematocrit <32%.
2. Abnormal hepatic function findings:
    a. AST/ALT >1.5 × upper limit of reference range and
    b. Albumin <lower limit of reference range.
3. Abnormal renal function: eGFR <30 mL/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; and
    e. Severe headaches, fatigue and problems concentrating.

In addition, during the MTX Run-in Period, if minor clinical symptoms emerge, such as mild stomatitis or mild gastrointestinal discomfort, the Investigator may increase the folic acid dose from 1 mg/day to 2 mg/day and/or reduce the MTX dose (but to no less than 15 mg/week). If symptoms improve, the subject will not be considered a screen failure on the basis of that symptom.

During the Pegloticase + MTX Treatment Periods, MTX dose guidance based on new laboratory findings or new symptoms will be as follows:

Table 9.2 Methotrexate Dose Guidance Based on New Laboratory Findings or New Symptoms

Parameter/Finding	Value	Methotrexate Dose Change
White blood cell count	≥3.0 to <3.5 × 10^9/L	Decrease from 25 mg to 20 or 15 mg OR Decrease from 15 mg to 10 mg
	<3.0 × 10^9/L	Decrease to 7.5 mg or temporary stop at discretion of the Investigator
Platelet count	≥50 to <75 × 10^9/L	Decrease from 25 mg to 20 or 15 mg OR No change if on 15 mg
	<50 × 10^9/L	Decrease to 7.5 mg or temporary stop at discretion of the Investigator
Hematocrit	<27%	Decrease to 7.5 mg or temporary stop at discretion of the Investigator
Alanine aminotransferase/ aspartate aminotransferase	>1.5 to ≤2 × ULN	Decrease from 25 mg to 20 or 15 mg OR Decrease from 15 mg to 10 mg
	>2 × ULN	Decrease to 7.5 mg or temporary stop at discretion of the Investigator
Estimated glomerular filtration rate	≥30 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2	Decrease from 25 mg to 20 or 15 mg OR No change if on 15 mg
	<30 mL/min/1.73 m^2	Decrease to 7.5 mg or temporary stop at discretion of the Investigator
New clinically important symptoms/signs[1]	Yes	Decrease to 7.5 mg or temporary stop at discretion of the Investigator

ULN = upper limit of normal

1. Rash or oral ulceration; persistent nausea, vomiting and diarrhea; new or increasing dyspnea or dry cough, or unexplained cough with fever; severe sore throat, abnormal bruising; severe headaches, fatigue, and problems concentrating; any other important medical event that might increase methotrexate toxicity or pre-dispose to new or worsening infection (e.g., surgery, hospitalization, treatment with antibiotics, clinical infection, developing new clinically significant pericardial/pleural effusion or ascites).

In addition, the Investigator may increase the folic acid dose from 1 mg/day to 2 mg/day. If, after more than 1 week of taking 2 mg/day folic acid, the sign/symptom or laboratory abnormalities do not resolve or improve, the subject is allowed to switch to oral leucovorin at 10 mg/week, given 10 to 24 hours POST each MTX injection, at discretion of the Investigator. In such case, the Investigator should discuss the timing of oral leucovorin administration relative to the MTX injection with the Medical Monitor to ensure subject compliance. Leucovorin taken before, at the time of or too soon (<8 hours) after MTX injection will likely reduce the efficacy of MTX.

Investigators should discuss the emergence of any 1 of the following criteria with the Medical Monitor to review the case:

1. ALT/AST >1.5 × ULN on 3 of any 5 consecutive measures;
2. Albumin <0.8 × lower limit of normal on 2 consecutive measures; and

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 Principal Investigator.

Guidance for increasing MTX back towards 15 or 25 mg/week after dose reduction, based on improvement or resolution of abnormal liver enzymes (>2 × ULN):

1. When liver enzymes return to ≤1.5 × ULN, increase MTX dose to the next available higher dose provided (i.e., 7.5 to 10 mg, 10 to 15 mg, 15 to 20 mg or 20 to 25 mg) and reassess in 2 weeks.
2. If liver enzymes remain ≤1.5 × ULN, increase MTX dose to the next available higher dose provided (i.e., 10 to 15 mg, 15 to 20 mg or 20 to 25 mg) and reassess in 2 weeks.

Improvement of other laboratory abnormalities potentially attributed to MTX may also warrant titration back up to 15 or 25 mg weekly, based on Principal Investigator judgement and in discussion with the Sponsor Medical Monitor.

9.4.7 Method of Assigning Subjects to Treatment Groups

All subjects will receive the same trial drugs (i.e., SC MTX and pegloticase).

Two sequential cohorts of subjects will be enrolled in this trial. Subjects who previously failed to maintain sUA response with pegloticase monotherapy and stopped pegloticase treatment without a history of pegloticase-related IR will be enrolled in Cohort 1.

The Safety Review Team will use the tolerability criteria to determine if Cohort 1 enrollment can continue, Cohort 2 enrollment can begin and whether subjects without a history of pegloticase-related clinically mild IR can enroll in Cohort 2.

Based on the safety assessment during Cohort 1, the trial can begin enrolling Cohort 2 if the pegloticase infusions are well tolerated or the trial will cease to screen and enroll new subjects if the pegloticase infusions are not well tolerated.

Subjects with a history of pegloticase-related clinically mild IR will be enrolled in Cohort 2. If the safety assessment during Cohort 2 indicates that the pegloticase infusions are not well tolerated based on pre-determined tolerability criteria or in the absence of subjects with a history of pegloticase-related clinically mild IR, the trial will continue with enrolling subjects without a history of pegloticase-related clinically mild IR.

9.4.8 Blinding

All trial drugs will be administered in an open-label fashion.

9.4.9 Prior and Concomitant Therapy

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

to the Screening Visit. Detailed pegloticase use history, including reason for discontinuation and associated reactions, if any, will be collected.

Concomitant medications are defined as drug or biological products other than the trial 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. If a subject is treated with antibiotics, refer to Section 9.4.6.3.2.2 for monitoring guidelines.

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.

Other than restricted medications (Section 9.4.10), other medications used at the time of trial initiation may be continued at the discretion of the Investigator.

9.4.9.1 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 trial will be prescribed anti-inflammatory treatment (e.g., NSAID, colchicine, corticosteroids and intra-articular steroid injections), as 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 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.

9.4.9.2 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-separator 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.

- When possible, a 12-lead electrocardiogram (ECG) will also be performed at the time of IR.

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 anaphylaxis criteria (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. All changes to infusion rate or dilution are to be recorded in the medical record and in the eCRF.

9.4.10 Restricted Medications

Subjects will be directed to discontinue current urate-lowering therapy at least 7 days prior to Day 1.

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

- Concomitant therapy with allopurinol, febuxostat, probenecid or other urate-lowering medications or a PEG-conjugated drug (see Appendix 17.10);
- Other investigational agents;

- Any MTX other than the trial approved investigational product, azathioprine, mycophenolate mofetil or other systemic immunosuppressants aside from glucocorticoids for gout flare or IR prophylaxis or intermittent gout flare treatment;
- Systemic or radiologic treatment for ongoing cancer, excluding non-melanoma skin cancer; and
- Current or chronic treatment with systemic immunosuppressive agents.

9.4.11 Treatment Compliance

A dosing calendar will be provided to subjects at the Week -6 Visit for recording the MTX dose and the date, time and mg dose of each dose. The dosing calendar and MTX auto-injector should be brought to each trial visit for assessment of compliance. At the end of the trial or if the subject prematurely discontinues the trial, the subjects will return any unused or partially used trial drugs to the site. Adherence to the MTX regimen will also be recorded by the trial coordinator at trial 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 injected at least 80% of the protocol-specified amount of MTX will be considered compliant. Noncompliant subjects will be re-educated on compliance.

At trial visits, the subject will be asked whether folic acid, gout flare and IR prophylaxis were administered.

Pegloticase will be administered at the trial site by trained personnel. The date and time of infusion start and stop and the stop and start time of the flush will be recorded.

9.4.12 Contraception Requirements

Women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening or not surgically sterile [absence of ovaries and/or uterus]) must agree to use 2 reliable forms of contraception during the trial, 1 of which is recommended to be hormonal, such as an oral contraceptive.

Hormonal contraception must be started ≥1 full cycle prior to Week -6 (start of MTX) and continue for 30 days after the last dose of pegloticase, or at least 1 ovulatory cycle after the last dose of MTX (whichever is the longer duration after the last dose of pegloticase). 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 trial, beginning with the initiation of MTX at Week -6 and continuing for at least 3 months after the last dose of MTX. Appropriate contraception methods include condom use and abstinence.

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

The Schedule of Assessments is provided in Section 2.1.

9.5.1 Efficacy Variables

Efficacy will be assessed based on measurement of sUA levels, urate deposition and CCI [redacted] and the HAQ-DI, HAQ pain scale and HAQ health scale.

9.5.1.1 Serum Uric Acid

Serum samples for measurement of sUA levels will be collected at the Screening Visit, the Week -6 Visit (prior to the first dose of MTX) and the Week -2 Visit. On Day 1, a pre- and post-infusion sUA will be collected to be shipped to the central laboratory. For the remainder of trial visits beginning at Week 2 during the Pegloticase + MTX Treatment Period; 2 sUA samples will be collected within 48 hours PRIOR to each pegloticase infusion. One sample will be for testing at the site's local laboratory and the second sample will be sent to the central laboratory (the central laboratory sample may be drawn separately from the local collection). The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours PRIOR to the infusion and the results of at least 1 sample are available prior to the infusion. Additional serum samples for sUA levels will be collected after the end of each pegloticase infusion prior to discharge at Weeks 10, 12, 14, 20, 22, 32, 34, 44 and 46; at Weeks 21 and 23; and at the End of Pegloticase (if applicable) or the Week 24 or 48/End of Trial/Early Termination Visit.

Serum for sUA analysis will also be collected following the first 7 pegloticase infusions at Day 1, Week 2, Week 4, Week 6, Week 8, Week 10 and Week 12, respectively. The sUA will be collected at the following non-infusion days: 1st (~24 hours), 4th (~96 hours), 7th (~168 hours) and 10th (~240 hours) day after each of the first 4 infusions, Day 1 to Week 6. Following Week 8, Week 10, Week 12, sUA will be collected at the following non-infusion days: 1st (~24 hours) and 7th (~168 hours). If infusion intervals of less than 2 weeks should occur due to scheduling issues, less than 4 sUA measurements between infusions are acceptable. The 1st day (~24hours) samples must be obtained at a minimum. If there are restrictions in relation to obtaining the interim samples also obtain 7th day (~168 hours) if feasible.

To ease the on-site visit burden for subjects, for non infusion visit sUA collection, a Home Health Care nurse may collect sUA samples, AE data and concomitant medication information if the subject consents

Prior to Week 22, subjects whose lowest available interim sUA value (typically the 1st day [~24 hours] after infusion) after the pegloticase infusion at Week 2, 4, 6, 8, 10 or 12 is less than a 50% reduction from the highest sUA value measured between Screening and pre-infusion on Day 1 will discontinue treatment and complete the End of Pegloticase Visit within 2 weeks of the last infusion, but remain in the trial for biweekly visits, including the Week 24/End of Trial/Early Termination and 30-Day Post-Treatment Follow-up Visits.

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 trial or proceed to the End of Pegloticase Visit.

9.5.1.2 Dual-energy Computed Tomography

A DECT (at a minimum, hands, feet and knees; other anatomical areas, as clinically indicated) will be obtained during the MTX Run-in Period and prior to the Day 1 Visit; prior to pegloticase infusion at the Week 14 and Week 24 Visits; and at the End of Pegloticase (if applicable) and Week 24 or 48/End of Trial/Early Termination Visits. After the initial DECT scan, the DECT at all other scheduled time points may be completed within ±10 days of the scheduled time point.

Subjects who end pegloticase infusions prior to Week 24 should follow the scheduled time points and have a DECT scan at the End of Pegloticase (if applicable) and Week 24/End of Trial/Early Termination Visits (detailed guidance is provided within the Imaging Manual).

The imaging will be performed by a trial-specific, qualified radiologist.

9.5.1.3 CCI

[redacted]

9.5.1.4 CCI

[redacted]

CCI

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

9.5.1.6 Health Assessment Questionnaire

The HAQ (Appendix 17.2) including the HAQ-DI, pain and health scales, will be administered at the Week -6 Visit (prior to the first dose of MTX); prior to pegloticase infusion at the Day 1, Weeks 6, 14 and 20 Visits (Pegloticase + MTX Treatment Period); prior to pegloticase infusion at the Weeks 24 and 36 Visits (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period); and at the End of Pegloticase (if applicable) and Week 24 or 48/End of Trial/Early Termination Visits (Section 2.1).

The HAQ-DI is a self-report functional status instrument that can be filled out by a subject in less than 5 minutes and requires 1 minute to score. The index measures disability over the past week by asking a total of 20 questions covering 8 domains of function: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. There are at least 2 questions in each domain and the 8 domains represent a comprehensive set of functional activities. The HAQ-DI is calculated by scoring the answer to each question in the HAQ from 0 to 3, with 0 representing the ability to do without any difficulty, and 3 representing inability to do. Any activity that requires assistance from another individual or requires the use of an assistive device raises a 0 or 1 score to a 2. The highest score for each of the 8 domains is summed (range from 0 to 24) and divided by 8 to yield, on a scale with 25 possible values, a Functional Disability Index with a range from 0 to 3. The disability index is based on the number of domains answered and is computed only if the subject completes answers to at least 6 domains (Bruce and Fries, 2003).

The HAQ pain scale 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.

9.5.1.7 CCI [redacted]

CCI [redacted]

CCI

9.5.2 CCI

CCI

9.5.2.1 CCI

CCI

9.5.2.2 CCI

CCI

CCI

9.5.2.3 CCI

CCI

9.5.3 CCI

Serum samples for CCI will be collected after the end of infusion on Day 1 (prior to discharge); prior to the pegloticase infusion and after the end of infusion (prior to discharge) at the Weeks 2, 6, 14 and 22 Visits (Pegloticase + MTX Treatment Period); prior to the pegloticase infusion and after the end of infusion at the Week 36 Visit (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period); and at the End of Pegloticase (if applicable) or Week 24 or 48/End of Trial/Early Termination Visit.

Serum samples for evaluation of CCI will be collected at the Week -6 Visit (prior to the first dose of MTX); prior to the pegloticase infusion on Day 1 and at the Weeks 2, 6, 14 and 22 Visits (Pegloticase + MTX Treatment Period); prior to the pegloticase infusion and after the end of infusion at the Week 36 Visit (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period); and at the End of Pegloticase (if applicable) or Week 24 or 48/End of Trial/Early Termination Visit.

Blood samples for CCI analysis will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 14 and 22 Visits (Pegloticase + MTX Treatment Period) and prior to the pegloticase infusion at the Weeks 24, 36 and 46 Visits (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period).

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

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

9.5.3.1 Additional Sample Collection for Future Use

Optional serum and urine samples will be collected from each consenting subject at the Week -6 Visit (prior to the first dose of MTX); prior to pegloticase infusion at the Day 1 and Week 14

Visits (Pegloticase + MTX Treatment Period); prior to pegloticase infusion at the Week 24 and Week 36 Visits (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period); and at the End of Pegloticase (if applicable) and Week 24 or 48/End of Trial/Early Termination Visits.

Subjects may still participate in the trial even if they decline to provide consent for the optional future use of serum and urine samples.

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

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

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

9.5.4 Safety Variables

Safety 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 and urine test.

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 trial subject administered a medicinal (investigational or non-investigational) product, whether or not the event is considered related to the trial drug. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding, except for an abnormal sUA result), symptom, or disease (new or exacerbated) temporally associated with the use of the trial 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 trial;
- Conditions known to have been present prior to the start of the trial that worsen after the signing of the ICF;
- Signs, symptoms or the clinical sequelae of a suspected drug interaction; and

- 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 trial 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 trial that do not represent a clinically significant change from Baseline; and
- 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 should usually be considered serious. Examples of such events are invasive cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of drug dependency or drug abuse. If in doubt as to whether or not an event qualifies as an 'important medical event,' consult the Sponsor's Medical Monitor.

9.5.4.1.1.3 Non-Serious Adverse Event Definition

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

9.5.4.1.1.4 Unexpected Adverse Event Definition

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

9.5.4.1.1.5 Adverse Events of Special Interest

AESIs include IRs, anaphylaxis, gout flares and MACE. If 3 events of Anaphylaxis (as assessed by PI) occur an Adjudication Committee (composed of independent experts external to Horizon) will be established for this trial to adjudicate AESI's of Anaphylaxis. The AESI of IR, MACE and gout flare will not be adjudicated.

Tolerability Criteria

Safety assessments of IR and anaphylaxis will be conducted after 7and 10 subjects in Cohort 1 complete 6 infusions and after 3, 6, 10,15 and 20 subjects in Cohort 2 complete 6 infusions. If more than one-third of subjects experience a severe IR and/or anaphylaxis related to pegloticase infusion, the pegloticase infusions will be considered not tolerated.

The signs and symptoms of severe IRs are usually prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion) or recurrent following initial improvement. Possible associated signs and symptoms of IRs may include, but not be limited to:

- Respiratory: difficulty breathing with wheezing or stridor; respiratory distress manifested as at least 2 or more of the following: tachypnoea, increased use of accessory respiratory muscles, cyanosis, recession or grunting;
- Upper airway swelling (lip, tongue, throat, uvula or larynx);
- Cardiovascular: hypertension, tachycardia, measured hypotension, a decreased level of consciousness or loss of consciousness;
- Dermatological or mucosal: generalized urticaria (hives), generalized erythema, angioedema or generalized pruritus with skin rash

The Safety Review Team must confirm that the tolerability criteria are not met in Cohort 1, prior to Screening subjects with history of pegloticase-related mild IR for Cohort 2. The Safety Review Team could stop the trial for other significant safety concerns.

If an anaphylaxis event occurs in any subject, further dosing with pegloticase for that subject will be discontinued. Anaphylaxis events will be adjudicated using the Sampson criteria (see Appendix **Error! Reference source not found.** for guidance on anaphylaxis and IR symptoms and assessment).

Infusion Reaction

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

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

In the event of any potential or suspected IR, the procedures in Section 9.4.9.2 will be performed.

Anaphylaxis

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives; pruritus or flushing; urticaria, and angioedema (of lips, tongue or uvula) and ≥1 of the following:

    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) or
    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 or 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); or
    d. Persistent gastrointestinal symptoms (e.g., crampy, abdominal pain, vomiting).

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

Gout Flares

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

Cardiovascular Events

Cardiovascular AEs will be collected as part of the AE collection. External adjudication will be conducted for MACE (defined as non-fatal stroke, non-fatal myocardial infarction, cardiovascular death and congestive heart failure). Refer to the Adjudication Committee Charter for the detailed definition.

9.5.4.1.2 Documentation of Adverse Events

AE and SAE monitoring will begin from the signing of the ICF until the 30-Day Post-Treatment Follow-up Visit.

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

9.5.4.1.3 Intensity of Adverse Events

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

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

9.5.4.1.4 Relationship to Trial 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 trial, 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 contacts provided below.

Fax CCI [redacted]
E-mail clinicalsafety@horizontherapeutics.com

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

1. Report the SAE to the Sponsor as outlined above.
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. Horizon or designee is responsible for the preparation of MedWatch 3500 A/Council for International Organizations of Medical Sciences I forms and analysis of similar events for individual occurrences (to be submitted as Investigational New Drug safety letters to the FDA and Investigators according to 21 CFR 312.32 by Horizon).

9.5.4.1.5.2 Product Complaints

A product complaint process will be described in the Trial 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 30-Day Post-Treatment Follow-up Visit should be reviewed to determine if further follow up is required. The Investigator will document on the AE eCRF all ongoing non-serious AEs that will not be followed further after the 30-Day Post-Treatment Follow-up Visit. 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 trial subject, at a dose above that which is assigned to that individual subject according to the trial 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 trial drug, as required by the applicable regulations. Investigators will notify their IRB of all such notifications, as required.

9.5.4.1.9 Reporting of Investigational New Drug 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 trial; however, any pregnancy complications, including an elective termination for medical reasons, should be reported as an AE.

Information must be obtained and reported if a female subject suspects that she has become pregnant during the trial (including the MTX Run-in Period) up to 30 days after the last dose of trial treatment (either pegloticase or MTX), or if a female partner of male subject suspects that she has become pregnant during the trial (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 trial 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, the female subject will be removed from pegloticase therapy and should remain in the trial unless she withdraws consent for trial participation. Pregnancy will be followed until the outcome of pregnancy is available.

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-trial pregnancy and considered reasonably related to the trial drug by the Investigator should be reported to the Sponsor.

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

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 recorded at the Screening Visit.

9.5.4.4 Vital Signs, Height and Weight

Routine vital signs, including blood pressure, respiratory rate, temperature and heart rate will be measured at Screening, Weeks -6, -4 and -2 (MTX Run-in Period), Day 1, Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22 (Pegloticase + MTX Treatment Period), Weeks 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44 and 46 (for subjects who participate in the Optional Pegloticase + MTX Extension Period) and the End of Pegloticase (if applicable), Week 24 or 48/End of Trial/Early Termination Visits. Heart rate and blood pressure measurements should be taken after the subject has been in a sitting position in a rested and calm state with proper positioning, including back support and feet flat on the floor, for at least 5 minutes. The subject's arm should be supported at heart level and the 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 trial visit. The Korotkoff phase V will be

used to determine diastolic blood pressure. During the Pegloticase + MTX Treatment Period visits, vital signs 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 blood pressure measurements for a given subject.

Weight should be measured in kilograms or pounds when the subject is not wearing shoes and recorded at the Screening Visit, prior to pegloticase infusion on Day 1, prior to pegloticase infusion at the Week 24 (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period) and at the End of Pegloticase (if applicable) or Week 24 or 48/End of Trial/Early Termination Visits.

Height will be collected at the Screening Visit only.

Vital sign monitoring during IR is described in Section 9.4.9.2.

9.5.4.5 Physical Examinations

A complete physical examination will be performed at the Screening Visit, including head, eyes, ears, nose and throat; heart; lungs; abdomen; skin; extremities; neurological status and musculoskeletal system. The examination will include assessment for presence of tophi, as well as gout history and symptom severity.

A targeted physical examination per Investigator judgement will be conducted at the Week -2 Visit and prior to administration of pegloticase on Day 1 and at the Weeks 4, 8, 12, 16 and 20 Visits (Pegloticase + MTX Treatment Period); prior to pegloticase infusion at the Weeks 24 and 36 Visits (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period); and at the End of Pegloticase (if applicable) or Week 24 or 48/End of Trial/Early Termination Visits; at a minimum the targeted physical examination should include heart, lungs and abdominal examination (Section 2.1).

Physical examination findings at Screening will be recorded on the appropriate 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 at Screening and will be read at the site.

When possible, a 12-lead ECG will also be performed at the time when a select AESI (see Section 9.5.4.1.1.5) is suspected.

9.5.4.7 Clinical Laboratory Safety Tests

A blood sample for G6PD analysis will be collected at the Screening Visit. G6PD testing should be performed by the central laboratory; however, if performed by the local laboratory, normal ranges should be provided.

Blood samples (for hematology and clinical chemistry) will be collected at the Screening Visit; at the Week -2 Visit; prior to the pegloticase infusion on Day 1 and at the Weeks 2, 6 and 14 Visits (Pegloticase + MTX Treatment Period); prior to pegloticase infusion at the Week 24 and 36 Visits (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period); and at the End of Pegloticase (if applicable) or Week 24 or 48/End of Trial/Early Termination Visits.

Urine samples (for albumin:creatinine ratio) will be collected at the Screening Visit; prior to the pegloticase infusion on Day 1 and at the Weeks 2, 6 and 14 Visits (Pegloticase + MTX Treatment Period); prior to pegloticase infusion at the Week 24 and 36 Visits (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period); and at the End of Pegloticase (if applicable) and Week 24 or 48/End of Trial/Early Termination Visits.

Women of childbearing potential (as defined in Section 9.5.4.2) will have a serum pregnancy test at the Screening Visit; urine samples (for human chorionic gonadotropin) will be collected at all other visits.

Safety laboratory assessments will include:

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

- Chemistry: albumin, transaminases (AST, ALT), alkaline phosphatase, total bilirubin, creatinine (including calculation for eGFR calculated by the MDRD equation: $175 \times (\text{standardized serum creatinine}_{[mg/dL]})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$ or $175 \times (\text{standardized serum creatinine}_{[\mu mol/L]}/88.4)^{-1\ 154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$, glucose, sodium, potassium, calcium, chloride, total protein and blood urea nitrogen; and

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

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

Blood samples for hs-CRP will be collected at the Screening Visit; prior to the pegloticase infusion on Day 1 and at the Week 14 Visits (Pegloticase + MTX Treatment Period); prior to pegloticase infusion at the Week 24 and 36 Visits (subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX

Extension Period); and at the End of Pegloticase (if applicable) and Week 24 or 48/End of Trial/Early Termination Visits.

9.5.4.8 Assessment of Gout Flare

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

9.5.5 Safety Review Team

Safety assessments of IR and anaphylaxis from available subjects' data will be performed by the Safety Review Team (comprising members of the Horizon Clinical Development and Patient Safety and Pharmacovigilance Teams) based on pre-determined tolerability criteria.

Depending on any potential safety signals reported (e.g., serious IR or any SAE related to pegloticase infusion), regular quarterly and/or ad hoc safety assessments will be conducted during the trial as specified in the Safety Management Plan and the Safety Review Team Charter.

9.5.6 Adjudication Committee

An Adjudication Committee (composed of independent experts external to Horizon) will be established for this trial to adjudicate the AESIs of anaphylaxis, if 3 events of Anaphylaxis (as assessed by PI) occur (see Section 9.5.4.1.1.5). The AESI of IR, MACE and gout flare will not be adjudicated. The AESIs of anaphylaxis will be adjudicated at a frequency defined in the Adjudication Committee Charter. The committee will be comprised of physicians with experience in immunology, allergic reactions, rheumatology and cardiovascular diseases. Details outlining the responsibilities of the Adjudication Committee will be included in the Adjudication Committee Charter.

9.5.7 Appropriateness of Measurements

The trial assessments are appropriate for a trial in subjects with gout and consistent with those used in registrational trials.

9.5.8 Trial Procedures

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

9.5.8.1 Screening Visit (Within 42 Days Prior to the First Dose of MTX at Week -6)

During the Screening Period, trial candidates will be evaluated for eligibility according to the stated inclusion and exclusion criteria (Section 9.3). The following procedures will be performed during Screening to establish each candidate's eligibility for participation into the trial.

- Obtain signed, written informed consent. Refusal to provide this permission excludes an individual from eligibility for trial participation. Record date informed consent was given and who conducted the process on the appropriate source documentation.

- Determine trial eligibility through review of the inclusion/exclusion criteria (see Section 9.3).

- Obtain demographic information.

- Chest x-ray for subjects who have not had a chest x-ray within 2 years prior to Screening if deemed necessary by the Investigator.

- Perform a complete physical examination, including assessment of head, eyes, ears, nose and throat; heart; lungs; abdomen; skin; extremities; neurological status and musculoskeletal system including an assessment for the presence of tophi as well as gout history and symptom severity (on gout-specific case report form).

- Collect prior pegloticase treatment history on pegloticase treatment case report form.

- 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 the screening, substance use history, and all other medications currently be taken at screening (see Section 9.4.10 for restrictions regarding medications).

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).

- Record height and weight.

- Perform 12-lead ECG.

- Obtain blood samples for hematology and clinical chemistry analysis and eGFR calculation (calculated by the central laboratory).

- Obtain a urine sample for urine albumin:creatinine ratio.

- Obtain a serum sample for pregnancy testing from female subjects of childbearing potential.

- Obtain blood samples to evaluate sUA (only 1 sUA sample for central laboratory).

- Obtain a blood sample for hs-CRP.

- Obtain a blood sample for G6PD.

- Inquire about AEs and concomitant medication use.

9.5.8.2 MTX Run-in Period

- A DECT scan will be obtained. The initial DECT scan will be performed after the Screening Visit, during the MTX Run-in Period and prior to the Day 1 Visit.

9.5.8.2.1 Week -6

- Confirm trial eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Principal Investigator review of subject clinical status and treatment goals.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Obtain blood samples to evaluate sUA (only 1 sample for central laboratory).
- CCI [redacted]
- Administer HAQ-DI, CCI [redacted]
- Record CCI [redacted].
- Obtain optional serum and urine samples from subjects who consent for future analysis.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Fill folic acid prescription.
- Dispense MTX with instructions to take it weekly (see Section 9.4.1 for dosing instructions).
- Obtain blood samples for CCI [redacted] prior to the first dose of MTX.
- Inquire about AEs and concomitant medication use.

9.5.8.2.2 Week -4

- Confirm trial eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX (see Section 9.4.1 for dosing instructions).
- Ask Yes/No question regarding folic acid compliance.
- Fill folic acid prescriptions, as needed.
- Inquire about AEs and concomitant medication use.
- Subjects who inject MTX during Week -6 or Week -5 and are females of childbearing potential will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of MTX to verify that at least 1 ovulatory cycle has occurred since the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. For subjects who are non-vasectomized males, an inquiry will be conducted approximately 3 months after MTX discontinuation regarding partner pregnancy.

9.5.8.2.3 Week -2

- Confirm trial eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- 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 pregnancy testing from female subjects of childbearing potential.
- Obtain a blood sample for measurement of sUA (only 1 sample for central laboratory).
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX (see Section 9.4.1 for dosing instructions).
- Ask Yes/No question regarding folic acid compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Inquire about AEs and concomitant medication use.
- Subjects who inject MTX during Week -4 or Week -3 and are females of childbearing potential will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of MTX to verify that at least 1 ovulatory cycle has occurred since the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. For subjects who are non-vasectomized males, an inquiry will be conducted approximately 3 months after MTX discontinuation regarding partner pregnancy.

9.5.8.3 Pegloticase + MTX Treatment Period

9.5.8.3.1 Day 1

Pre-infusion Day 1

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

- Confirm trial eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Enroll subjects without a history of pegloticase-related IR in Cohort 1 (see Section 9.4.7).
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).

- Record weight.
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- CCI .
- Administer HAQ-DI, CCI
- Record CCI .
- Obtain optional serum and urine samples from subjects who consent for future analysis.
- Obtain blood samples for hematology and clinical chemistry analysis and eGFR calculation (calculated by the central laboratory).
- Obtain a urine sample for albumin:creatinine ratio.
- Obtain blood samples to evaluate sUA (only 1 sample for central laboratory).
- Obtain blood samples to evaluate hs-CRP.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Obtain blood samples for CCI .
- Obtain blood samples for CCI .
- Administer IR prophylaxis (see Section 9.4.1.5).
- Subjects who inject MTX during Week -2 or Week -1 and are females of childbearing potential will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of MTX to verify that at least 1 ovulatory cycle has occurred since the last

dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. For subjects who are non-vasectomized males, an inquiry will be conducted approximately 3 months after MTX discontinuation regarding partner pregnancy.

- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 1st dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and start/stop times of the 10 ml flush.

Post-infusion Day 1

On Day 1, the following assessments will be performed after the pegloticase infusion.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

- Obtain blood sample for CCI after the end of the infusion, prior to discharge from the site.

- Obtain 1 blood sample for measurement of sUA after the end of the pegloticase infusion for shipment to the central laboratory.

- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 1st day (~24 hours) after the pegloticase infusion.

- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 4th day (~96 hours) after the pegloticase infusion.

- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 7th day (~168 hours) after the pegloticase infusion.

9.5.8.3.2 Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 10th day (~240 hours) after the pegloticase infusion. Week 2

Pre-infusion Week 2

At Week 2, subjects will return to the clinic for the following assessments prior to the 2nd dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 2 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be

drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).

- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Obtain blood samples for hematology and clinical chemistry analysis and eGFR calculation (calculated by the central laboratory).
- Obtain a urine sample for albumin:creatinine ratio.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Obtain blood samples for CCI [redacted].
- Obtain blood sample for CCI [redacted] analysis.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 2nd dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 2

At Week 2, the following assessments will be performed after the pegloticase infusion.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).
- Obtain blood sample for CCI [redacted] after the end of the infusion, prior to discharge from the site.
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 1st day (~24 hours) after the pegloticase infusion.
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 4th day (~96 hours) after the pegloticase infusion.
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 7th day (~168 hours) after the pegloticase infusion.
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 10th day (~240 hours) after the pegloticase infusion.
    - Stopping rule: Subjects whose lowest available interim sUA value (typically the 1st day [~24 hours] after infusion) after the pegloticase infusion at Week 2 is less than a 50% reduction from the highest sUA value measured between Screening and pre-infusion on Day 1 will discontinue treatment and complete the End of Pegloticase Visit within 2 weeks of the last infusion, but remain in the trial for biweekly visits, including the Week 24/End of Trial/Early Termination and 30-Day Post-Treatment Follow-up Visits.

9.5.8.3.3 Week 4

Pre-infusion Week 4

At Week 4, subjects will return to the clinic for the following assessments prior to the 3rd dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 4 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).

- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 3rd dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 4

At Week 4, the following assessment will be performed after the pegloticase infusion.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 1st day (~24 hours) after the pegloticase infusion.

- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 4th day (~96 hours) after the pegloticase infusion.

- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 7th day (~168 hours) after the pegloticase infusion.

- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 10th day (~240 hours) after the pegloticase infusion.

    - Stopping rule: Subjects whose lowest available interim sUA value (typically the 1st day [~24 hours] after infusion) after the pegloticase infusion at Week 4 is less than a 50% reduction from the highest sUA value measured between Screening and pre-infusion on Day 1 will discontinue treatment and complete the End of Pegloticase Visit within 2 weeks of the last infusion, but remain in the trial for biweekly visits, including the Week 24/End of Trial/Early Termination and 30-Day Post-Treatment Follow-up Visits.

9.5.8.3.4 Week 6

Pre-infusion Week 6

At Week 6, subjects will return to the clinic for the following assessments prior to the 4th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 6 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).

- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.

- CCI [redacted].

- Administer HAQ-DI.

- Obtain blood samples for hematology and clinical chemistry analysis and eGFR calculation (calculated by the central laboratory).
- Obtain a urine sample for albumin:creatinine ratio.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Obtain blood samples for CCI [redacted].
- Obtain blood sample for CCI [redacted] analysis.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 4th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 6

At Week 6, the following assessments will be performed after the pegloticase infusion.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).
- Obtain blood sample for CCI [redacted] after the end of the infusion, prior to discharge from the site.
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 1st day (~24 hours) after the pegloticase infusion.

- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 4th day (~96 hours) after the pegloticase infusion.

- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 7th day (~168 hours) after the pegloticase infusion.

- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 10th day (~240 hours) after the pegloticase infusion.

    - Stopping rule: Subjects whose lowest available interim sUA value (typically the 1st day [~24 hours] after infusion) after the pegloticase infusion at Week 6 is less than a 50% reduction from the highest sUA value measured between Screening and pre-infusion on Day 1 will discontinue treatment and complete the End of Pegloticase Visit within 2 weeks of the last infusion, but remain in the trial for biweekly visits, including the Week 24/End of Trial/Early Termination and 30-Day Post-Treatment Follow-up Visits.

9.5.8.3.5 Week 8

Pre-infusion Week 8

At Week 8, subjects will return to the clinic for the following assessments prior to the 5th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 8 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).

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

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).

- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.

- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.

- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 5th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 8

At Week 8, the following assessment will be performed after the pegloticase infusion.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 1st day (~24 hours) after the pegloticase infusion.
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 7th day (~168 hours) after the pegloticase infusion.
    - Stopping rule: Subjects whose lowest available interim sUA value (typically the 1st day [~24 hours] after infusion) after the pegloticase infusion at Week 8 is less than a 50% reduction from the highest sUA value measured between Screening and pre-infusion on Day 1 will discontinue treatment and complete the End of Pegloticase Visit within 2 weeks of the last infusion, but remain in the trial for biweekly visits, including the Week 24/End of Trial/Early Termination and 30-Day Post-Treatment Follow-up Visits.

9.5.8.3.6 Week 10

Pre-infusion Week 10

At Week 10, subjects will return to the clinic for the following assessments prior to the 6th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 10 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 6th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 10

At Week 10, the following assessment will be performed after the pegloticase infusion.

- Obtain a blood sample (1 sample) for measurement of sUA by the central laboratory after the end of pegloticase infusion, prior to discharge.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 1st day (~24 hours) after the pegloticase infusion.
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 7th day (~168 hours) after the pegloticase infusion.
    - Stopping rule: Subjects whose lowest available interim sUA value (typically the 1st day [~24 hours] after infusion) after the pegloticase infusion at Week 10 is less than a 50% reduction from the highest sUA value measured between Screening and pre-infusion on Day 1 will discontinue treatment and complete the End of Pegloticase Visit within 2 weeks of the last infusion, but remain in the trial for biweekly visits, including the Week 24/End of Trial/Early Termination and 30-Day Post-Treatment Follow-up Visits.

9.5.8.3.7 Week 12

Pre-infusion Week 12

At Week 12, subjects will return to the clinic for the following assessments prior to the 7th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 12 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 7th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 12

At Week 12, the following assessment will be performed after the pegloticase infusion.

- Obtain a blood sample (1 sample) for measurement of sUA by the central laboratory after the end of pegloticase infusion, prior to discharge.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 1st day (~24 hours) after the pegloticase infusion
- Obtain blood sample to evaluate sUA (only 1 sample for central laboratory) on the 7th day (~168 hours) after the pegloticase infusion.

- Stopping rule: Subjects whose lowest available interim sUA value (typically the 1st day [~24 hours] after infusion) after the pegloticase infusion at Week 12 is less than a 50% reduction from the highest sUA value measured between Screening and pre-infusion on Day 1 will discontinue treatment and complete the End of Pegloticase Visit within 2 weeks of the last infusion, but remain in the trial for biweekly visits, including the Week 24/End of Trial/Early Termination and 30-Day Post-Treatment Follow-up Visits.

9.5.8.3.8 Week 14

Pre-infusion Week 14

At Week 14, subjects will return to the clinic for the following assessments prior to the 8th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 14 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Obtain blood samples for hematology, clinical chemistry and hs-CRP analysis and eGFR calculation (calculated by the central laboratory).
- Obtain a urine sample for albumin:creatinine ratio.
- CCI [redacted].
- Administer HAQ-DI, CCI [redacted]
- Record CCI [redacted].
- Obtain optional serum and urine samples from subjects who consent for future analysis.

- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Obtain blood samples for CCI [redacted] analysis.
- Obtain blood samples for CCI [redacted].
- Obtain blood sample for CCI [redacted].
- Administer IR prophylaxis (see Section 9.4.1.5).
- A DECT scan will be obtained. DECT may be completed within ±10 days of the scheduled visit.
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 8th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 14

At Week 14, the following assessments will be performed after the pegloticase infusion.

- Obtain a blood sample (1 sample) for measurement of sUA by the central laboratory after the end of pegloticase infusion, prior to discharge.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).
- Obtain blood sample for CCI [redacted] after the end of the infusion, prior to discharge from the site.

9.5.8.3.9 Week 16

Pre-infusion Week 16

At Week 16, subjects will return to the clinic for the following assessments prior to the 9th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 16 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 9th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 16

At Week 16, the following assessment will be performed after the pegloticase infusion.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.3.10 Week 18

Pre-infusion Week 18

At Week 18, subjects will return to the clinic for the following assessments prior to the 10th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 18 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.

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

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

- Administer IR prophylaxis (see Section 9.4.1.5).

- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 10th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 18

At Week 18, the following assessment will be performed after the pegloticase infusion.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.3.11 Week 20

Pre-infusion Week 20

At Week 20, subjects will return to the clinic for the following assessments prior to the 11th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 20 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).

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

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).

- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- CCI [redacted].
- Administer HAQ-DI.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 11th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 20

At Week 20, the following assessment will be performed after the pegloticase infusion.

- Obtain a blood sample (1 sample) for measurement of sUA by the central laboratory after the end of pegloticase infusion, prior to discharge.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.3.12 Week 21

At Week 21, subjects will return to the clinic for the following assessments.

- Obtain a blood sample for measurement of sUA by the central laboratory.

- Document gout flares and intensity.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Inquire about AEs and concomitant medication use.

9.5.8.3.13 Week 22

Pre-infusion Week 22

At Week 22, subjects will return to the clinic for the following assessments prior to the 12th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 22 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis and IR prophylaxis compliance.

- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed for subjects who may gain further benefit beyond 12 infusions and elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period.

- Obtain blood samples for CCI [redacted] analysis.

- Obtain blood samples for CCI [redacted].

- Obtain blood sample for CCI [redacted].

- Administer IR prophylaxis (see Section 9.4.1.5).

- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 12th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 22

At Week 22, the following assessments will be performed after the pegloticase infusion.

- Obtain a blood sample (1 sample) for measurement of sUA by the central laboratory after the end of pegloticase infusion, prior to discharge.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

- Obtain blood sample for CCI [redacted] after the end of the infusion, prior to discharge from the site.

9.5.8.3.14 Week 23

At Week 23, subjects will return to the clinic for the following assessments.

- Obtain a blood sample for measurement of sUA by the central laboratory.

- Document gout flares and intensity.

- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.

- If subject has not injected MTX within the previous 1 to 3 days, administer MTX.

- Inquire about AEs and concomitant medication use.

At the discretion of the Principal Investigator, subjects who may gain further benefit may elect to receive pegloticase + MTX during the Optional Pegloticase + MTX Extension Period and will receive additional infusions at Weeks 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44 and 46.

9.5.8.3.15 Week 24/1st Infusion of Optional Pegloticase + MTX Extension Period

Week 24 is the final visit of the Pegloticase + MTX Treatment Period. Subjects who may not gain further benefit beyond 12 infusions based on the Principal Investigator's judgement and decide to complete the study at Week 24 (see Section 9.5.1.1) or who discontinue treatment prior to Week 22 will complete the End of Pegloticase Visit (see Section 9.5.8.4). Trial drug is not administered for subjects who may not gain further benefit beyond 12 infusions based on the Principal Investigator's judgement.

For subjects who may gain further benefit beyond 12 infusions and elect to receive trial drug, the infusion will be performed at Week 24.

Pre-infusion Week 24

At Week 24, subjects will return to the clinic for the following assessments prior to the 13th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 14 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Principal Investigator review of subject clinical status and treatment goals.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Record weight.
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.

- Obtain blood samples for hematology, clinical chemistry and hs-CRP analysis and eGFR calculation (calculated by the central laboratory).
- Obtain a urine sample for albumin:creatinine ratio.
- CCI .
- Administer HAQ-DI, CCI
- Record CCI .
- Obtain optional serum and urine samples from subjects who consent for future analysis.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis and IR prophylaxis compliance.
- Fill gout prophylaxis, IR prophylaxis and folic acid prescriptions, as needed.
- Obtain blood samples for CCI .
- Obtain blood sample for CCI .
- Obtain blood samples for CCI analysis.
- Administer IR prophylaxis (see Section 9.4.1.5).
- A DECT scan will be obtained. DECT may be completed within ±10 days of the scheduled visit.
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 13th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 24

At Week 24, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.4 End of Pegloticase Visit

Subjects who end pegloticase infusions prior to Week 22 will complete the End of Pegloticase Visit procedures within 2 weeks of their final infusion. Subjects are especially encouraged to complete trial visits at the trial site for key efficacy and safety assessments at Weeks 10, 12, 14, 20, 21, 22, 23 and 24/End of Trial/Early Termination, so that sUA and other key assessments can be completed. During visits between these key efficacy and safety collection visits, in subjects who have stopped infusions, subjects may complete trial visits in person or via a telephone visit to collect AE, concomitant medication and gout flare information (see Section 9.3.3.1.1).

For subjects who agree to continue trial visits after the End of Pegloticase Visit, the 30-Day Post Treatment Follow-up Visit will be captured as part of the continued visits; however, if the last trial visit is <30 days posttreatment, the 30-Day Post-Treatment Follow-up phone call/email will still be required.

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

- Principal Investigator review of subject clinical status and treatment goals.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) prior to discharge (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Obtain optional serum and urine samples from subjects who consent for future analysis.
- Obtain blood samples for hematology, clinical chemistry and hs-CRP analysis and eGFR calculation (calculated by the central laboratory).
- Obtain a urine sample for albumin:creatinine ratio.

- Obtain a blood sample (1 sample) for measurement of sUA.
- Administer MTX (subjects who have not stopped pegloticase due to individual subject sUA discontinuation criteria).
- Assess MTX compliance/reconciliation.
- CCI .
- Administer HAQ-DI, CCI
- Record CCI .
- If handheld uric acid device is provided, assess Investigator or subject user experience with uric acid device questionnaire at any time during the visit prior to discharge from the site.
- Assess MTX compliance.
- Ask Yes/No question regarding folic acid compliance.
- Ask Yes/No question regarding gout flare prophylaxis compliance.
- A DECT scan may be performed ±10 days from the scheduled visit date. Subjects who end pegloticase infusions prior to Week 24 should follow the scheduled time points and have a DECT scan at the Week 24/End of Trial/Early Termination Visits.
- Obtain blood samples for CCI .
- Obtain blood sample for CCI .
- Inquire about AEs and concomitant medication use.

9.5.8.5 Optional Pegloticase + MTX Extension Period Visits After Week 24 - Subjects Who May Gain Further Benefit Beyond 12 Infusions

9.5.8.5.1 Week 26

Pre-infusion Week 26

At Week 26, subjects will return to the clinic for the following assessments prior to the 14th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 26 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).

- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.

- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.

- Assess MTX compliance/reconciliation.

- Re-dispense MTX.

- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.

- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.

- Administer IR prophylaxis (see Section 9.4.1.5).

- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 14th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 26

At Week 26, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.5.2 Week 28

Pre-infusion Week 28

At Week 28, subjects will return to the clinic for the following assessments prior to the 15th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 28 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).

- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.

- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.

- Assess MTX compliance/reconciliation.

- Re-dispense MTX.

- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.

- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.

- Administer IR prophylaxis (see Section 9.4.1.5).

- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 15th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 28

At Week 28, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.5.3 Week 30

Pre-infusion Week 30

At Week 30, subjects will return to the clinic for the following assessments prior to the 16th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 30 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).

- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.

- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.

- Assess MTX compliance/reconciliation.

- Re-dispense MTX.

- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.

- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.

- Administer IR prophylaxis (see Section 9.4.1.5).

- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 16th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 30

At Week 30, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.5.4 Week 32

Pre-infusion Week 32

At Week 32, subjects will return to the clinic for the following assessments prior to the 17th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 32 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.
- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 17th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 32

At Week 32, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Obtain a blood sample (1 sample) for measurement of sUA by the central laboratory after the end of pegloticase infusion, prior to discharge.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.5.5 Week 34

Pre-infusion Week 34

At Week 34, subjects will return to the clinic for the following assessments prior to the 18th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 34 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- .
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.

- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.
- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 18th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 34

At Week 34, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Obtain a blood sample (1 sample) for measurement of sUA by the central laboratory after the end of pegloticase infusion, prior to discharge.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.5.6 Week 36

Pre-infusion Week 36

At Week 36, subjects will return to the clinic for the following assessments prior to the 19th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 36 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Principal Investigator review of subject clinical status and treatment goals.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Obtain blood samples for hematology, clinical chemistry and hs-CRP analysis and eGFR calculation (calculated by the central laboratory).
- Obtain a urine sample for albumin:creatinine ratio.
- CCI [redacted].
- Administer HAQ-DI, CCI [redacted]
- Record CCI [redacted].
- Obtain optional serum and urine samples from subjects who consent for future analysis.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.

- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.
- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.
- Obtain blood samples for CCI [redacted] analysis.
- Obtain blood samples for CCI [redacted].
- Obtain blood sample for CCI [redacted].
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 19th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 36

At Week 36, the following assessments will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).
- Obtain blood sample for CCI [redacted] after the end of the infusion, prior to discharge from the site.

9.5.8.5.7 Week 38

Pre-infusion Week 38

At Week 38, subjects will return to the clinic for the following assessments prior to the 20th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 38 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.
- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 20th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 38

At Week 38, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.5.8 Week 40

Pre-infusion Week 40

At Week 40, subjects will return to the clinic for the following assessments prior to the 21st dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 40 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).

- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.

- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.

- Assess MTX compliance/reconciliation.

- Re-dispense MTX.

- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.

- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.

- Administer IR prophylaxis (see Section 9.4.1.5).

- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 21st dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 40

At Week 40, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.5.9 Week 42

Pre-infusion Week 42

At Week 42, subjects will return to the clinic for the following assessments prior to the 22nd dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 42 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.
- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 22nd dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 42

At Week 42, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.5.10 Week 44

Pre-infusion Week 44

At Week 44, subjects will return to the clinic for the following assessments prior to the 23rd dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 44 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.
- Re-dispense MTX.
- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.
- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.
- Administer IR prophylaxis (see Section 9.4.1.5).
- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 23rd dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 44

At Week 44, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Obtain a blood sample (1 sample) for measurement of sUA by the central laboratory after the end of pegloticase infusion, prior to discharge.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.5.11 Week 46

Pre-infusion Week 46

At Week 46, subjects will return to the clinic for the following assessments prior to the 24th dose of pegloticase.

- Obtain 2 blood samples for measurement of sUA within 48 hours prior to the Week 46 pegloticase infusion. One sample will be tested for sUA at the site's local laboratory and 1 sample will be shipped to the central laboratory for testing. The local laboratory or central laboratory pre-infusion sUA results should be reported prior to pegloticase infusion. Note: It is allowable for the local and central laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion and the results of at least 1 sample are available prior to the infusion (see Section 9.5.1.1).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) (see Section 9.5.4.4).
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Provide dosing calendar for subjects to record the date and time they inject MTX. Additional calendar pages will be provided at future visits as needed.
- Assess MTX compliance/reconciliation.

- If subject has not injected MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis (for subjects who receive gout flare prophylaxis) and IR prophylaxis compliance.

- Fill gout prophylaxis (at the discretion of the Principal Investigator), IR prophylaxis and folic acid prescriptions, as needed.

- Obtain blood samples for CCI [redacted] analysis.

- Administer IR prophylaxis (see Section 9.4.1.5).

- Inquire about AEs and concomitant medication use.

INFUSION: Following completion of the above procedures, administer the 24th dose of pegloticase and record date, volume and duration of infusion and start/stop (IV infusion 120 ±15 minutes) times of dosing and the start/stop times of the 10 ml flush.

Post-infusion Week 46

At Week 46, the following assessment will be performed after the pegloticase infusion (for subjects who may gain further benefit with additional pegloticase treatment beyond 12 infusions based on the Principal Investigator's judgement).

- Obtain a blood sample (1 sample) for measurement of sUA by the central laboratory after the end of pegloticase infusion, prior to discharge.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) any time after the end of the infusion, but prior to subject's discharge/release from the site (see Section 9.5.4.4).

9.5.8.6 Week 24 or 48/End of Trial/Early Termination Visit

Subjects who may not gain further benefit beyond 12 infusions based on the Principal Investigator's judgement or who discontinue treatment prior to Week 22 will complete the procedures outlined below.

The following procedures will be completed at the Week 24 or 48/End of Trial/Early Termination Visit.

- Principal Investigator review of subject clinical status and treatment goals.

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

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature and heart rate) prior to discharge (see Section 9.5.4.4).
- Record weight.
- Obtain a urine sample for pregnancy testing from female subjects of childbearing potential.
- Obtain optional serum and urine samples from subjects who consent for future analysis
- Obtain blood samples for hematology, clinical chemistry and hs-CRP analysis and eGFR calculation (calculated by the central laboratory).
- Obtain a urine sample for albumin:creatinine ratio.
- Obtain a blood sample (1 sample) for measurement of sUA.
- Administer MTX (subjects who have not stopped pegloticase due to individual subject sUA discontinuation criteria).
- Assess MTX compliance/reconciliation.
- CCI [redacted].
- Administer HAQ-DI, CCI [redacted]
- Record CCI [redacted].
- Assess MTX compliance.
- Ask Yes/No question regarding folic acid and gout flare prophylaxis (for subjects who receive gout flare prophylaxis in the Optional Pegloticase + MTX Extension Period) compliance.
- Subjects who end pegloticase infusions prior to Week 24 or 48 should follow the scheduled time points and have a DECT scan at the Week 24 or 48/End of Trial/Early Termination Visits.
- Obtain blood samples for CCI [redacted].
- Obtain blood sample for CCI [redacted].
- Obtain blood samples for CCI [redacted] analysis.
- Inquire about AEs and concomitant medication use.

9.5.8.7 30-Day Post-Treatment Follow-up Phone/Email Visit

Thirty (30) days after the last MTX dose or pegloticase infusion (whichever is later), subjects will be contacted by telephone or email to review AEs, SAEs and concomitant medications. Subjects who receive at least 1 dose of MTX and are females of childbearing potential, will receive a safety follow-up phone call/e-mail approximately 4 weeks/30 days after the last dose of MTX to verify at least 1 ovulatory cycle has occurred after the last dose of MTX. If the subject has not ovulated, the subject will be requested to return to the site for a urine pregnancy test.

9.5.8.8 MTX Partner Pregnancy Follow-up

Male subjects who are non-vasectomized will be asked 3 months after MTX discontinuation regarding partner pregnancy.

9.6 Statistical Methods and Determination of Sample Size

9.6.1 Endpoints

9.6.1.1 Primary Endpoint

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

9.6.1.2 Secondary Endpoints

The secondary endpoints are:

- The proportion of Month 3 (Weeks 10 to 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 subjects who experienced any of the following events from Day 1 to Week 24: IR leading to discontinuation of treatment, anaphylaxis or meeting Individual Subject sUA Discontinuation Criteria.
- The mean change from Baseline in urate deposition volume (measured by DECT) to Week 24.
- The mean change from Baseline in HAQ-DI score at Weeks 14 and 24.
- The mean change from Baseline in HAQ pain score at Weeks 14 and 24.

- The mean change from Baseline in HAQ health score at Weeks 14 and 24.

9.6.1.3 Exploratory Endpoints

The exploratory endpoints are:

9.6.1.4 CCI

The CCI are:

- The concentrations of CCI over time.
- The incidence and titer of CCI over time.
- The concentrations of CCI over time.

9.6.1.5 Safety and Tolerability Endpoints

Safety and tolerability endpoints are:

- The incidence of IRs, anaphylaxis, gout flares, MACE and the AE/SAE profile overall and potentially attributed to the combination of pegloticase and MTX.
- The mean change from Baseline in laboratory test results, including hs-CRP.
- The mean change from Baseline in vital sign results.

9.6.2 Analysis Sets

The following analysis sets will be defined for this trial:

- MTX treated analysis set: all subjects who receive ≥1 dose of MTX.
- Intent-to-treat (ITT) analysis set: all enrolled subjects who receive ≥1 dose of pegloticase with MTX.
- Safety analysis set: all enrolled subjects who receive ≥1 dose of pegloticase with MTX.
- CCI [redacted] ≥1 [redacted].

9.6.3 Demographic Variables

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

9.6.4 Subject Disposition

The number of subjects in each analysis set and the number and percentage of subjects who complete the trial, who discontinue the trial prematurely, who complete pegloticase treatment and who discontinue treatment prematurely, along with the reasons for discontinuation will be summarized.

9.6.5 Efficacy Analysis

Data will be summarized descriptively. 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.

9.6.5.1 Primary and Secondary Endpoint Analysis

The estimand for the primary analysis will use the Treatment Policy Strategy for most intercurrent events; selected intercurrent events leading to data that are missing completely at random may be addressed with a While-on-Treatment Strategy (e.g., if site closures due to COVID-19).

The primary efficacy endpoint is the proportion of responders during Month 6. The proportion of time each subject's sUA is <6 mg/dL will be calculated using observed data at Weeks 20, 21, 22, 23 and 24. The amount of time that sUA is <6 mg/dL (using linear interpolation, if necessary) will be calculated and divided by the total amount of time from the first to the last observed sUA value in this time range (missed values in this time range will be ignored for purposes of this calculation). Subjects who have no available sUA value in this time range will be imputed as non-responders unless the data are missing completely at random, in which case they will be omitted from the analysis. Two-sided exact 95% confidence intervals (CIs) will be calculated.

The primary analysis will be performed on all enrolled subjects who receive ≥1 dose of pegloticase with MTX (i.e., the ITT analysis set).

The proportion of Month 3 responders will be summarized similarly to the Month 6 responders. All sUA results collected between infusions from Week 10 through Week 14 of the trial will be used in the calculation of the Month 3 responders.

The mean change from Baseline in in urate deposition volume (measured by DECT) to Week 24 will be summarized along with the corresponding 95% CI for subjects with DECT assessments.

The proportion of subjects experiencing any of the following events: IR leading to discontinuation of treatment, anaphylaxis or meeting Individual Subject sUA Discontinuation Criteria will be presented. For this composite endpoint, each individual component of the composite will be analyzed overall with a summary of the incidence and the corresponding 95% CI.

The primary and secondary endpoints will be summarized overall and by cohort. If Cohort 2 enrolls both subjects with previous mild IR and those with no previous IR, then the data will be summarized by IR category (no IR, mild IR) within Cohort 2 and for Cohorts 1 and 2 combined. No adjustments to CIs will be made for multiple endpoints or multiple time points.

9.6.5.2 Exploratory Endpoint Analysis

Exploratory endpoints (see Section 9.6.1.3) for CCI will be summarized using descriptive statistics.

9.6.6 CCI

Concentrations for CCI will be summarized by time point using descriptive statistics for the CCI and ITT analysis sets, respectively.

Incidence of CCI [redacted] will be summarized using the ITT analysis set.

The impact of CCI [redacted] will be explored.

9.6.7 Safety Analysis

Treatment-emergent AEs (TEAEs) during the MTX 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 + MTX Periods 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 will be summarized separately for the Run-in Period and the Pegloticase + MTX Treatment Period (inclusive of the Optional Pegloticase + MTX Extension Period). TEAEs in the Pegloticase + MTX Treatment Period will be summarized overall and by cohort. If Cohort 2 enrolls both subjects with previous mild IR and those with no previous IR, then the data will be summarized by IR category (no IR, mild IR) within Cohort 2 and for Cohorts 1 and 2 combined. AEs that occur more than 30 days after the last dose of pegloticase and/or MTX through the 30-Day Post-Treatment Follow-up Visit will also be summarized.

The number and percentage of subjects with at least 1 AE, at least 1 SAE, at least 1 severe AE and with an AE that leads to discontinuation of pegloticase and/or MTX will be summarized. Adverse events will be listed.

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

The proportion of subjects with SAEs and each AESI will also be summarized.

Laboratory test results will be summarized by trial 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 trial visit and change from Baseline.

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

9.6.8 Interim Analyses

Safety data will be summarized for safety assessments conducted after 7and 10 subjects in Cohort 1 complete 6 infusions and after 3, 6,10,15, and 20 subjects in Cohort 2 complete 6 infusions. The results of these analyses will determine if enrollment will continue in each

cohort. Efficacy and safety data may be summarized periodically throughout the trial to support scientific publications. Additionally, safety data will be summarized regularly for safety monitoring. Final analysis will occur when all subjects have completed the trial. No Type 1 error rate adjustments will be made due to multiple summaries.

9.6.9 Sample Size and Power Considerations

A sample size of 30 subjects is planned for this trial to provide a sizeable number of subjects to support the following projections. The primary efficacy endpoint will be demonstrated to be statistically greater than 20% if at least 12/30 (40%) responders are observed. In that case, the lower bound of a 95% CI for the proportion of responders will be approximately 23%.

9.7 Changes in the Conduct of the Trial

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

All protocol deviations and the reasons for such deviations **must** be documented in the eCRF.

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 trial and to ensure that trial data can be subsequently verified. These documents should be classified in 2 separate categories: (1) Investigator trial 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 trial center:

- Medical history/physical condition and diagnosis of the subject before involvement in the trial sufficient to verify that the subject meets protocol entry criteria.
- Trial 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 trial visit including each trial assessment and the identity of the staff member performing the assessment.
- Trial 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 trial.

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 trial 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 TRIAL MONITORING

The Investigator will ensure that the trial 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 trial 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 trial protocol and Investigator's Brochure to all Sub-Investigators, pharmacists and other staff responsible for trial conduct.

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

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

At intervals during the trial, as well as after the completion of subject enrollment, the trial center will be monitored by the Sponsor or designee for compliance. During these visits, the monitor will discuss trial 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 trial 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 trial 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 trial 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 trial. 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 trial and to have direct access to inspect, for purposes of verification, the hospital or clinical records of all subjects enrolled in this trial. 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 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 and AE/medical history/surgery/non drug therapy terms will be coded using the Rheumatology Common Toxicity Criteria v2.0.

14 RETENTION OF RECORDS

No trial documents at the trial 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 trial-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 trial-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 trial 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

Albert J, Hosey T, LaMoreaux B. Subcutaneous or oral methotrexate exposure and response to pegloticase in uncontrolled gout patients in a community rheumatology practice [abstract]. Arthritis Rheumatol. 2019;71:2131-2.

Ben-Horin S, Waterman M, Kopylov U, et al. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. Clin Gastro Hepatol. 2013:11:444-7.

Berhanu AA, Krasnokutsky S, Keenan RT, Pillinger MH. Pegloticase failure and a possible solution: Immunosuppression to prevent intolerance and inefficacy in patients with gout. Semin Arthritis Rheum. 2017;46:754-8.

Bessen SY, Bessen MY, Yung CM. Recapture and improved outcome of pegloticase response with methotrexate-A report of two cases and review of the literature. Semin Arthritis Rheum. 2019a;49:56-61.

Bessen MY, Bessen SY, Yung CM. Concomitant immunosuppressant use with pegloticase in patients with tophaceous gout - a case series. Int J Clin Rheumatol. 2019b;14:238-45.

Botson J, Peterson J. Pretreatment and co-administration with methotrexate improved durability of pegloticase response: a prospective observational, proof-of-concept, case series [abstract]. Ann Rheum Dis. 2019;78:A1289.

Botson JK, Tesser JRP, Bennett R, et al. Pegloticase in combination with methotrexate in patients with uncontrolled gout: A multicenter, open-label study (MIRROR). J Rheum. 2020 Sep 15. doi:10.3899/jrheum.200460.

Braun J, Kästner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arth Rheum. 2008;58:73-81.

Bressolle F, Bologna C, Kinowski JM, Sany J, Combe B. Effects of moderate renal insufficiency on pharmacokinetics of methotrexate in rheumatoid arthritis patients. Ann Rheum Dis. 1998;57(2):110-3.

Brook RA, Forsythe A, Smeeding JE, Lawrence Edwards N. Chronic gout: epidemiology, disease progression, treatment and disease burden. Curr Med Res Opin. 2010;26(12):2813-21.

Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes. 2003;1:20.

Burmester GR, Kivitz AJ, Kupper H, et al. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Ann Rheum Dis. 2015;74(6):1037-44.

Ceponis A, Kavanaugh A. Use of methotrexate in patients with psoriatic arthritis. Clin Exp Rheumatol. 2010;28(5 Suppl 61):S132-7.

CIMZIA (UCB Inc.). Certolizumab pegol for injection, for subcutaneous use. United States Prescribing Information. September 2019. https://www.cimzia.com/themes/custom/cimzia/docs/CIMZIA_full_prescribing_information.pdf

FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res (Hoboken). 2020;72:744-60.

Freyne B. A case report of immunosuppressant medication associated polyarticular tophaceous gout successfully treated using the polyethylene glycol-conjugated uricase enzyme pegloticase. Transplant Proc. 2018;50:4099-101.

Gaffo AL, Schumacher RH, Saag KG, et al. Developing a provisional definition of flare in patients with established gout. Arthritis Rheum. 2012;65(5):1508-17.

Hershfield MS, Ganson NJ, Kelly SJ, Scarlett EL, Jaggers DA, Sundy JS. Induced and pre-existing anti-polyethylene glycol antibody in a trial of every 3-week dosing of pegloticase for refractory gout, including in organ transplant recipients. Arthritis Res Ther. 2014;16:R63.

HUMIRA (AbbVie Inc.). Adalimumab injection, for subcutaneous use. United States Prescribing Information. October 2018. https://www.rxabbvie.com/pdf/humira.pdf

Keenan RT, Baraf HSB, LaMoreaux B. Use of pre-infusion serum uric acid levels as a biomarker for infusion reaction risk in patients on pegloticase. Rheumatol Ther. 2019;https://doi.org/10.1007/s40744-019-0151-9.

Khanna P, Khanna D, Storgard C, Baumgartner S, Morlock R. A world of hurt: failure to achieve treatment goals in patients with gout requires a paradigm shift. Postgrad Med. 2016;128(1):34-40.

Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis. 2012;71:1914-5.

KRYSTEXXA Full Prescribing Information.

KRYSTEXXA® Pegloticase (polyethylene glycol-uricase) Investigator's Brochure, Horizon Pharma, edition 10.0, 25 July 2018.

Lie E, Kristensen LE, Forsblad-d'Elia H, et al. The effect of comedication with conventional synthetic disease modifying antirheumatic drugs on TNF inhibitor drug survival in patients with ankylosing spondylitis and undifferentiated spondyloarthritis: results from a nationwide prospective study. Ann Rheum Dis 2015;74:970-8.

Masri K, Winterling K, LaMoreaux B. Leflunomide co-therapy with pegloticase in uncontrolled gout. Ann Rheum Dis. 2020;79:450.

Mease P. Methotrexate in psoriatic arthritis. Bull Hosp Jt Dis. 2013;71 Suppl 1:S41-5.

Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR, Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990 1999. Ann Rheum Dis. 2005;64(2):267-72.

Mouterde G, Baillet A, Gaujoux-Viala C, et al. Optimizing methotrexate therapy in rheumatoid arthritis: a systematic literature review. Joint Bone Spine. 2011;78(6):587-92.

Rainey H, Baraf HSB, Yeo A, Lipsky P. Companion immunosuppression with azathioprine increases the frequency of persistent responsiveness to pegloticase in patients with chronic refractory gout. Ann Rheum Dis. 2020;79:438.

REMICADE (Janssen Biotech, Inc.). Infliximab for injection, for intravenous use. United States Prescribing Information. May 2020. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf.

Roddy E, Doherty M. Epidemiology of gout. Arthritis Res Ther. 2010;12(6):223.

Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. Arthritis Res Ther. 2006;8 Suppl 1:S2.

Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008;59(6):762-84.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

Sattui SE, Singh JA, Gaffo AL. Comorbidities in patients with crystal diseases and hyperuricemia. Rheum Dis Clin North Am. 2014;40(2):251-78.

Schiff MH, Sadowski P. Oral to subcutaneous methotrexate dose-conversion strategy in the treatment of rheumatoid arthritis. Rheumatol Int. 2017;37:213-8.

Singh JA, Strand V. Gout is associated with more comorbidities, poorer health related quality of life and higher healthcare utilisation in US veterans. Ann Rheum Dis. 2008;67(9):1310-6.

Strand V, Balsa A, Al-Saleh J, et al. Immunogenicity of biologics in chronic inflammatory diseases: a systematic review. BioDrugs. 2017;31(4):299-316.

Strik AS, van den Brink GR, Ponsioen C, Mathot R, Lowenberg M, D'haens GR. Suppression of anti-drug antibodies to infliximab or adalimumab with the addition of an immunomodulator in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2017;45:1128-34.

Sundy JS, Baraf HS, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA. 2011;306(7):711-20.

Ungar B, Kopylov U, Engel T, et al. Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab. Aliment Pharmacol Ther. 2017;45:276-82.

Vena GA, Cassano N, Iannone F. Update on subcutaneous methotrexate for inflammatory arthritis and psoriasis. Ther Clin Risk Management. 2018;14:105-16.

Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis. 2009;68(7):1094-9.

Wertheimer A, Morlock R, Becker A. A revised estimate of the burden of illness of gout. Curr Ther Res Clin Exp. 2013;75:1-4.

Woodworth T, Furst DE, Alten R, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v2.0. J Rheumatol. 2007;34(6):1401-14.

Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011;63(10):3136-41.

17 APPENDICES

17.1 Administrative Appendix

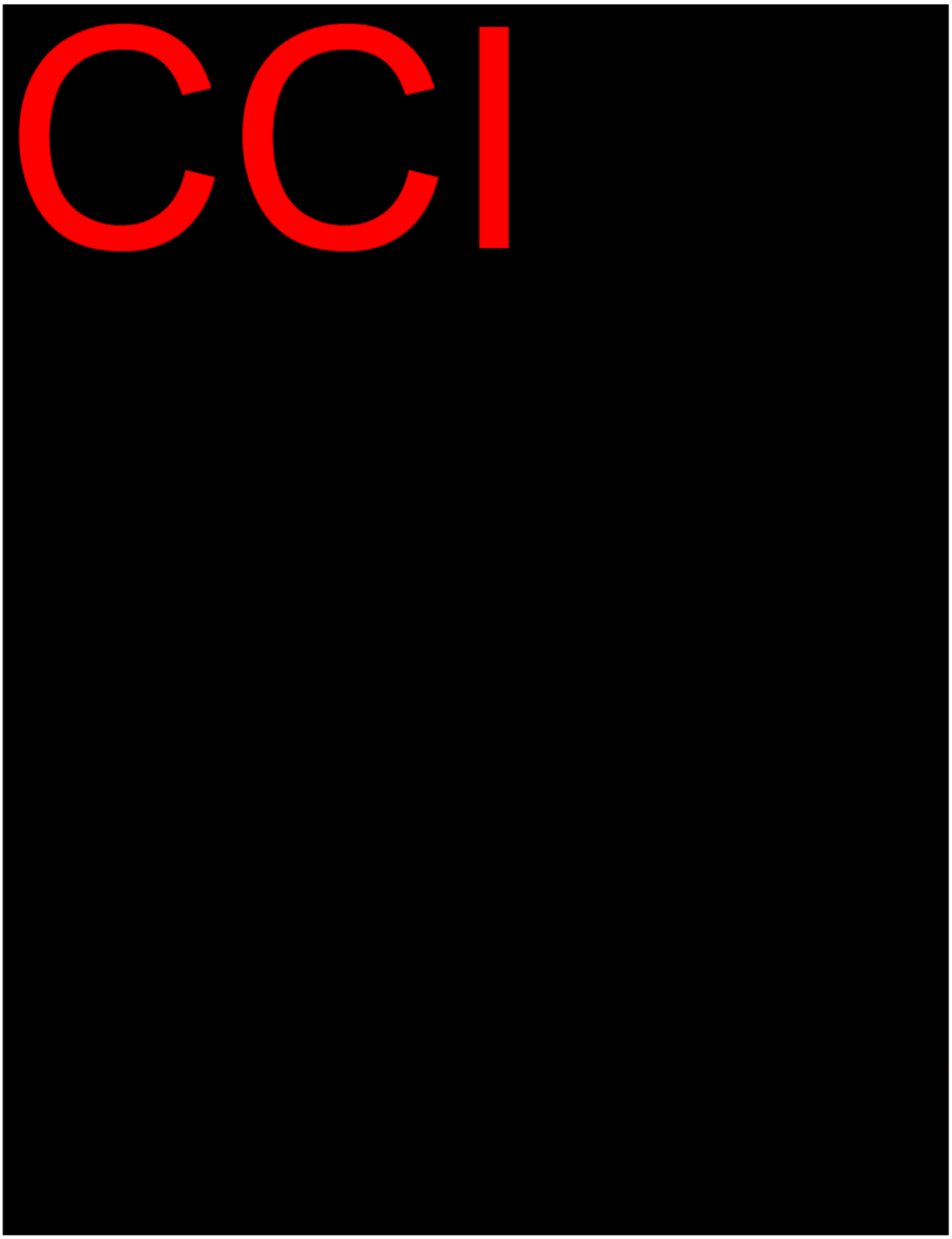
This appendix provides names and contact information for the trial administrative structure. The IRB must be notified of changes that are made to this section, but IRB review or approval of these changes is not required. Changes made in this section will be dated but will not be assigned a protocol amendment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

Clinical Monitor	PPD Horizon Therapeutics U.S.A., Inc. Two Tower Place, 12th Floor South San Francisco, CA 94080 Mobile telephone number: PPD Office telephone number: PPD Fax number: PPD Email: PPD
Sponsor Representative	PPD PPD Horizon Therapeutics Ireland DAC, 70 St. Stephen's Green Dublin, Ireland D02E2X4 Mobile telephone number: PPD Fax number: PPD Email:PPD
Sponsor Contact for Serious Adverse Event Reporting	ICON Fax number: PPD Email: clinicalsafety@horizontherapeutics.com
24-hour Phone Contact for Safety Coverage	Med Communications Phone number: PPD

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

Example HAQ-DI below. This page not for subject use. Horizon will supply the site with copies for subject use.

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

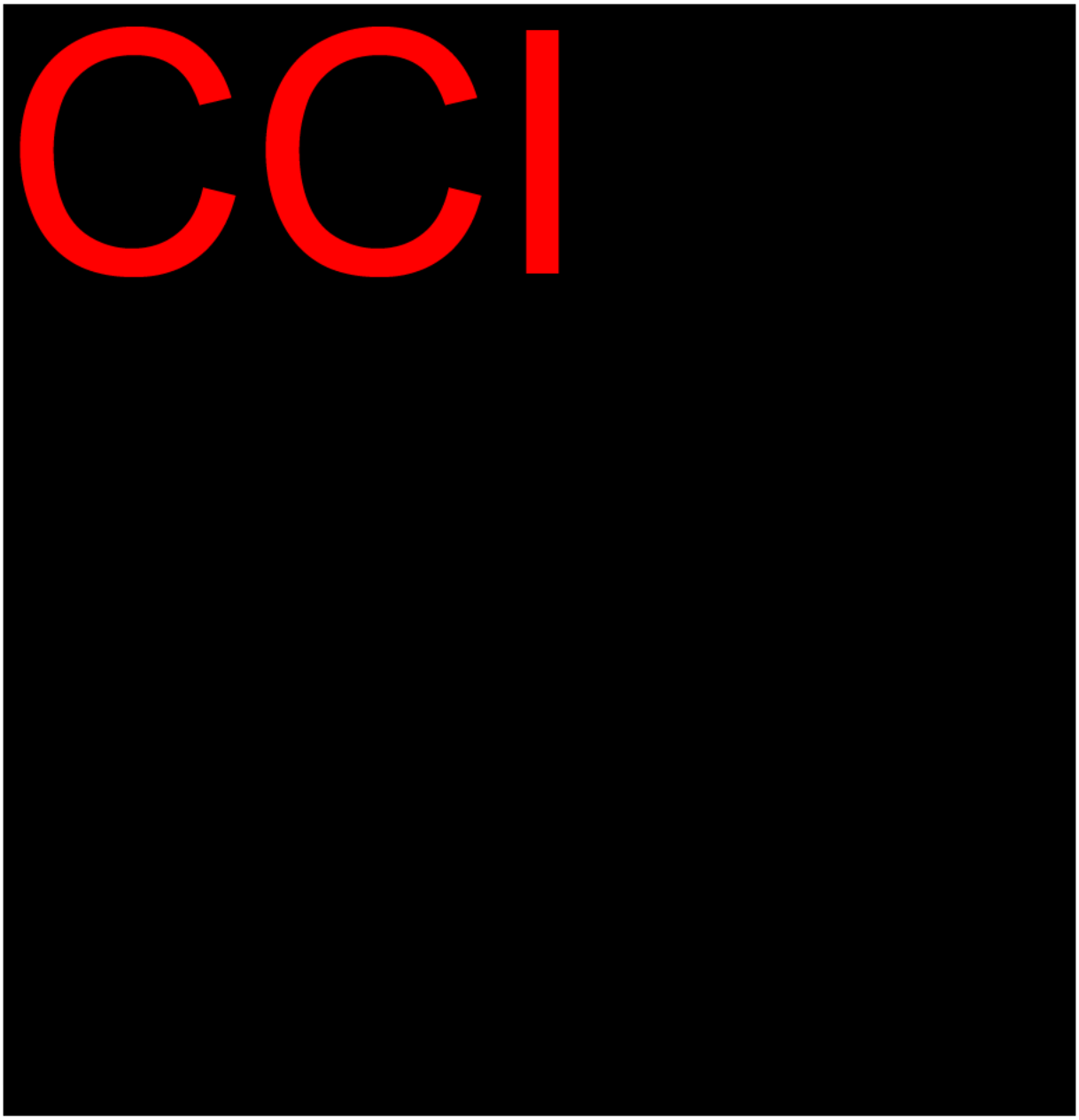

CCI


CCI

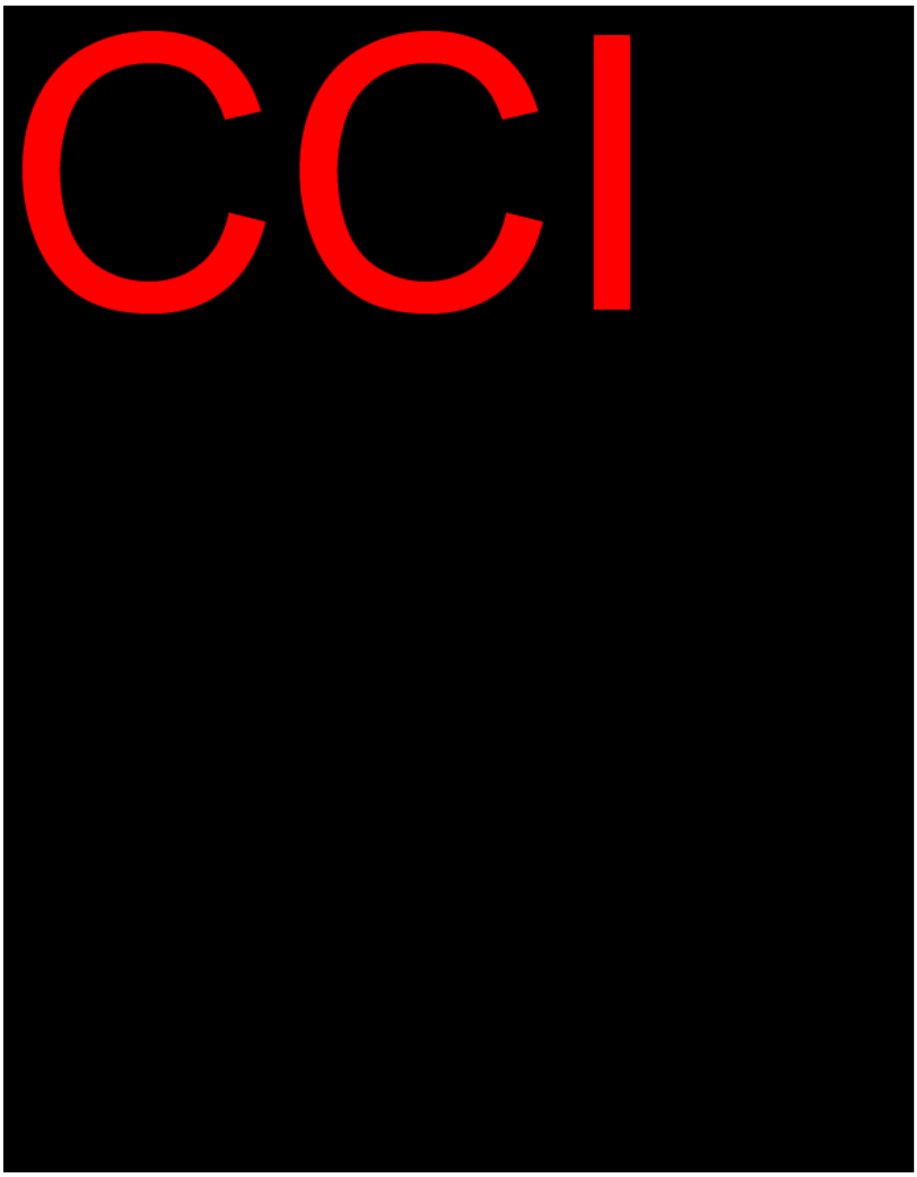
17.3 CCI

17.4 CCI

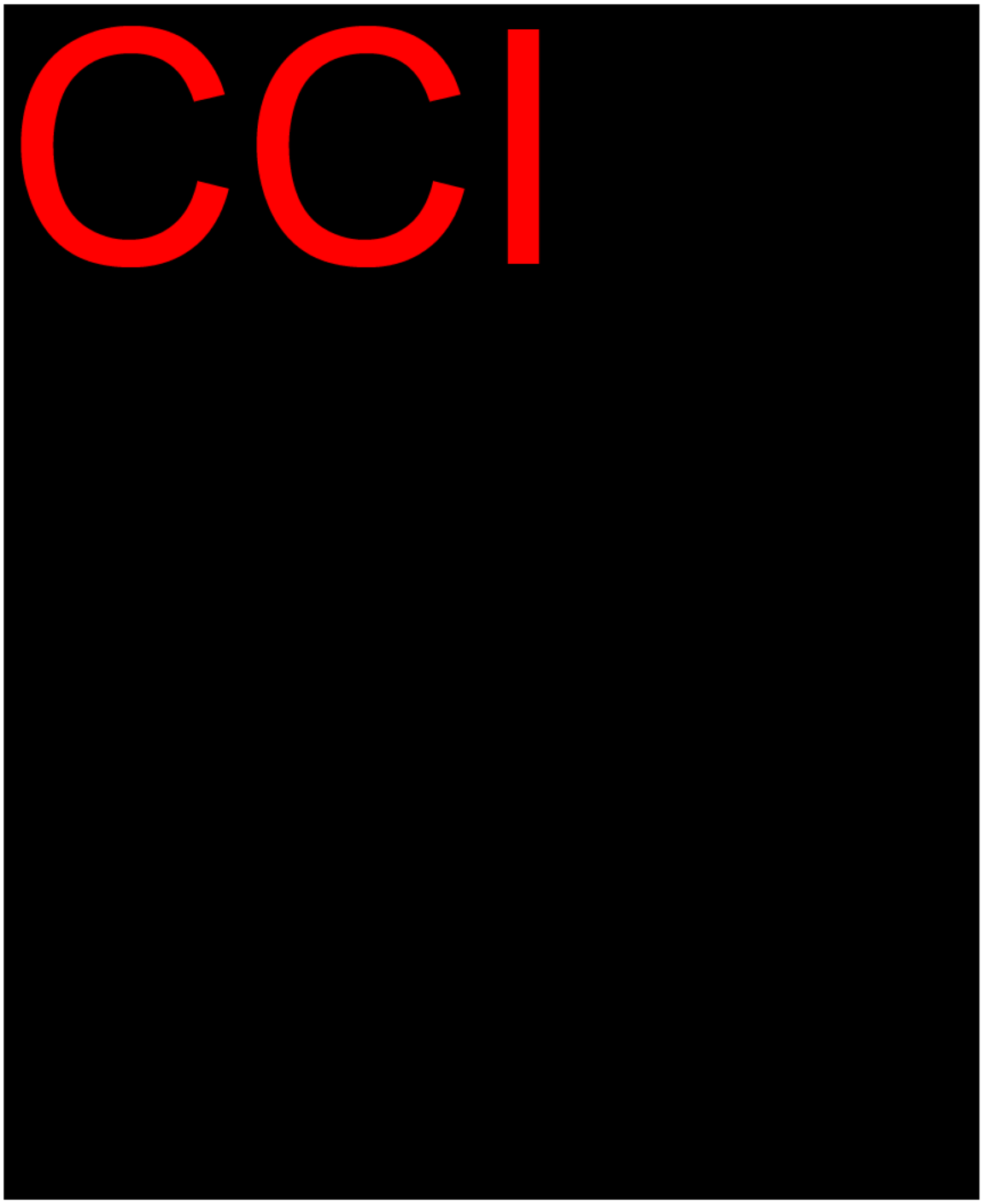
17.5 CCI

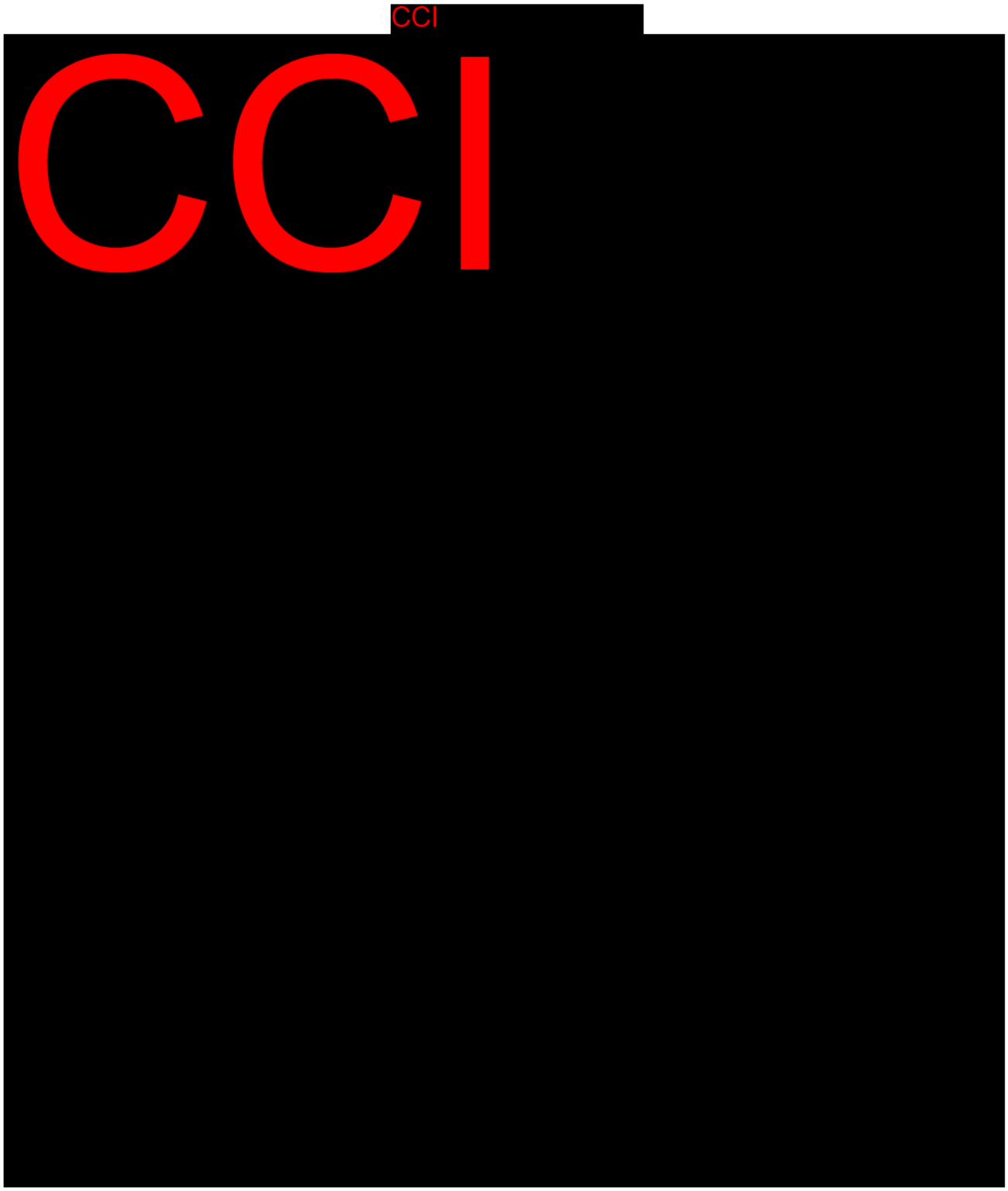

CCI

17.6 CCI



17.7 CCI

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17.8 CCI [redacted]

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17.9 Infusion Reaction and Anaphylaxis Assessment Guidance

1. Infusion Reaction Criteria and Severity Assessment Guidance

An infusion reaction (IR) will be defined as any infusion-related adverse event or cluster of temporally related adverse events, not attributable to another cause, which occur during the pegloticase infusion and for up to 2 hours post infusion. Other adverse events that occur outside of the 2-hour window and up to 24 hours following the infusion may also be categorized as an IR at the Principal Investigator's discretion.

In general, the severity assessment should follow the following Infusion Reaction Severity definition in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (Nov. 2017).

CTCAE term	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)	Grade 5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids)	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death

A Sponsor Adjudication Committee will review the signs, symptoms and treatment administered for the prior IR associated with pegloticase infusion before subjects with history of mild IR are enrolled in Cohort 2.

2. Anaphylaxis Criteria

Based on NIAID/FAAN (National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network) criteria by Sampson et al, 2006, anaphylaxis is likely when any 1 of the following 3 criteria are fulfilled:

- 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, swollen lips- tongue- uvula) with at least 1of the following
    - Respiratory compromise (e.g., dyspnea, wheeze- bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

  - Reduced blood pressure or associated symptoms of end- organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
- Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours)
  - Involvement of the skin- mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  - Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
  - Persistent gastrointestinal symptoms (e.g., crampy, abdominal pain, vomiting).
- The subject experiences a reduced blood pressure after exposure to a known allergen for that subject (minutes to several hours)
  - Systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that subject's Baseline.

17.10 Polyethylene Glycol-Conjugated Drug List

Concomitant use of other PEG-conjugated drugs including but not limited to those outlined below is prohibited from Screening through the end of pegloticase and MTX during the trial.

Brand Name	**Generic name or Parent protein**
ADAGEN®	Pegademase bovine
ADYNOVATE®	Factor VIII
CIMZIA®	Certolizumab pegol
DOXIL®	Doxorubicin
JIVI®	Factor VIII
MACUGEN®	Pegaptanib
MIRCERA®	Epoietin beta
MOVANTIK®	Naloxegol
NEULASTA®	Pegfilgrastim
OMONTYS®	Peginesatide
ONCASPAR®	Asparaginase
ONIVYDE	Irinotecan liposome
PALYNZIQ®	Pegvaliase-pqpz
PEGASYS®	PegInterferon alfa-2a
PEGINTRON®	PegInterferon alfa-2b
PLEGRIDY®	PegInterferon beta-1a
REBINYN®	Coagulation Factor IX
SOMAVERT®	Pegvisomant
SYLATRON®	PegInterferon alfa-2b