CLINICAL STUDY PROTOCOL FOR PEGLOTICASE

IND: 010122

Protocol Number: HZNP-KRY-406

Version 3.0, Amendment 2

A Multicenter, Open-Label, Efficacy and Safety Study of Pegloticase in Patients with Uncontrolled Gout Who Have Undergone Kidney Transplantation

Date: 22 June 2020

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

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CONFIDENTIAL

PROTOCOL

1 TITLE PAGE

Study Title:	A Multicenter, Open-Label, Efficacy and Safety Study of Pegloticase in in Patients With Uncontrolled Gout Who Have Undergone Kidney Transplantation
Protocol Number:	HZNP-KRY-406
Version:	3.0, Amendment 2
Investigational Products:	Pegloticase (recombinant modified mammalian urate oxidase [uricase])
Indication:	Chronic gout in adult patients refractory to conventional therapy
Sponsor:	Horizon Therapeutics Ireland DAC 1 Burlington Road Connaught House, 1st Floor Dublin Ireland D04 C5Y6
Development Phase:	4
Sponsor's Responsible Medical Officer:	[redacted] 150 S. Saunders Road Lake Forest, IL 60045
Sponsor Signatory:	[redacted] Horizon Therapeutics USA, Inc. 150 S. Saunders Road Lake Forest, IL 60045
Approval Date:	22 June 2020

CONTACT IN THE EVENT OF AN EMERGENCY

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

Fax: [redacted]
Email: [redacted]

SPONSOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-406

Version: 3.0, Amendment 2

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Version Date: 22 June 2020

Approved by: [redacted]

[redacted] Date

[redacted]
Horizon Therapeutics USA, Inc.

[redacted]

[redacted] Date

[redacted]
Horizon Therapeutics USA, Inc.

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-406

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

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

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

Signature:

_____ _____

Name Date
Study Center
Address
City State Country

SUMMARY TABLE OF CHANGES

Protocol Version 1.0, Original (10 JUN 2019) to
Protocol Version 2.0, Amendment 1 (21 JAN 2020)
Protocol Version 2.0, Amendment 1 (21 JAN 2020), Administrative Change 1 (31 MAR 2020)
Protocol Version 3.0, Amendment 2 (22 JUN 2020)

The table below highlights the changes to the objectives, statistical analysis and study design only. Administrative and typographical updates have also been made. Track changes version of the Protocol Version 3.0, Amendment 2 can be provided on request.

Text Version 2.0, Amendment 1, Administrative Change 1 31 MAR 2020	Amended Text Version 3.0, Amendment 2 22 JUN 2020	Reason for Change
Replacement Policy/Subject: Section 9.3.4.1 *No subject prematurely discontinued from the study for any reason will be replaced.*	**Replacement Policy/Subject: Section 9.3.4.1** *In general, subjects that prematurely discontinue from the study for any reason will not be replaced. An exception may be made for subjects who are unevaluable due to the impact of the 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 study to allow for the originally planned number to be evaluable for the primary efficacy analysis.*	*Updated due to the COVID-19 pandemic.*
9.3.4.3 Screen Failures *Subjects who do not meet all of the eligibility criteria or withdraw consent between Screening and Day 1 will be considered screen failures. Screen failures may be allowed to rescreen for the study if both the Investigator and Sponsor are in*	**9.3.4.3 Screen Failures** *Subjects who do not meet all of the eligibility criteria or withdraw consent between Screening and Day 1 will be considered screen failures. Screen failures may be allowed to rescreen for the study if both the Investigator and Sponsor are in agreement regarding*	*To clarify that screen failure subjects who consent to the optional blood draw for biomarker analysis will be requested to return to the clinic 24 weeks after screening for a second blood sample as well as assessment of adverse events,*

agreement regarding rescreening and if the Investigator determines that they can satisfy all of the eligibility criteria.	*rescreening and if the Investigator determines that they can satisfy all of the eligibility criteria.* *Subjects who fail screening but consented to the optional blood draw for biomarker analysis will be requested to return to the site 24 weeks +/- 4 weeks for a second blood sample. Adverse events, concomitant medications, blood samples for hematology and clinical chemistry and vital signs will vital signs will also be collected as an unscheduled visit at that time.*	*con meds, safety labs and vital signs.*
Section 9.6.5.1: Primary and Secondary Endpoint Analysis: *Sentence not previously included.*	**Section 9.6.5.1: Primary and Secondary Endpoint Analysis:** *Special consideration may be given to subjects who discontinue the study or miss visits due to reasons related to the COVID-19 pandemic.*	*Added language due to COVID-19 pandemic.*
Section 9.5.4.8: Blood and Urine Sample for Potential Analysis of Allantoin *Blood and urine samples will be collected prior to pegloticase infusion on Day 1 and at the Week 2, 4, 6, 8, 10, 14, 18, and 22 Visits, the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit, and the 3-month Post-Treatment Follow-up Visit. In addition, blood and urine samples will be collected after the end of pegloticase infusions prior to discharge from the site on Day 1, Week 2, 6, 14 and 22 Visits.*	**Section 9.5.4.8: Blood and Urine Sample for Potential Analysis of Allantoin** *Blood and urine samples will be collected prior to pegloticase infusion on Day 1 and at the Week 2, 4, 6, 8, 10, 14, 18, and 22 Visits, the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit, and the 3-month Post-Treatment Follow-up Visit. In addition, blood and urine samples will be collected after the end of pegloticase infusions prior to discharge from the site on Day 1, Week 2, 6, 14 and 22 Visits. Both allantoin and creatinine will be analyzed in urine samples collected at these visits to calculate allantoin:creatinine ratio.*	*Added analysis of urine creatinine at same time points as urine allantoin for measurement of allantoin:creatinine ratio.*
Section 9.5.4.9: Blood Samples for Potential Analysis of Biomarkers *Optional blood samples for peripheral blood mononuclear cells (PBMC) and serum will be collected from each consenting*	**Section 9.5.4.9: Blood Samples for Potential Analysis of Biomarkers** *Optional blood samples for peripheral blood mononuclear cells (PBMC) and serum will be collected from each consenting subject at Screening, the Week 8 and 14 Visits, the End-of-*	*To clarify that screen failure subjects who consent to the optional blood draw for biomarker analysis will be requested to return to the clinic 24 weeks after screening for a second blood sample as well as assessment of adverse events,*

subject at Screening, the Week 8 and 14 Visits, the End-of-Pegloticase-Infusions Visit (if applicable), and the Week 24/End-of-Study/Early Termination Visit. Subjects who fail Screening will also be requested to provide at least 1 additional blood sample approximately 20-24 after the initial sample collection.	*Pegloticase-Infusions Visit (if applicable), and the Week 24/End-of-Study/Early Termination Visit. Subjects who fail Screening will also be requested to provide at least 1 additional blood sample 24 weeks +/- 4 weeks after the initial sample collection. An unscheduled visit will be arranged at that time to also collect adverse events, concomitant medications, blood samples for hematology and clinical chemistry and vital signs.*	*con meds, safety labs and vital signs.*

2 SYNOPSIS

Protocol Title: A Multicenter, Open-label, Efficacy and Safety Study of Pegloticase in Patients With Uncontrolled Gout Who Have Undergone Kidney Transplantation	
Protocol Number: HZNP-KRY-406	**Phase:** 4
Protocol Version: 3.0, Amendment 2	
Test Drugs: Pegloticase	**Indication**: Chronic gout refractory to conventional therapy in adult patients
Number subjects and Number and Country of Study Sites: Twenty subjects at approximately 15 study centers in the United States	

Objectives:

The overall objective of the study is to assess the efficacy and safety of pegloticase in kidney transplant subjects with uncontrolled gout refractory to conventional urate lowering therapy.

Primary Objective:

To evaluate the effect of pegloticase on the response rate of sustained serum uric acid (sUA) reduction to sUA <6 mg/dL during Month 6 of treatment

Secondary Objectives:

To evaluate the effect of pegloticase on the response rate of sustained serum uric acid reduction to sUA <5 mg/dL during Month 6 of treatment;

To evaluate the effect of pegloticase on pain assessed by the Health Assessment Questionnaire (HAQ) pain score; and

To evaluate the effect of pegloticase on disability assessed by the Health Assessment Questionnaire - Disability Index (HAQ-DI) score.

Exploratory Objectives:

[redacted]

To evaluate the pharmacokinetics (PK) of pegloticase and the profile of anti- monomethoxy-poly(ethylene glycol) (PEG) and anti-uricase IgG antibodies; and

To evaluate the safety and efficacy 3 months after the end of treatment with pegloticase

Safety Objectives:

To assess the overall adverse event (AE)/serious AE (SAE) profile including AEs of special interest (AESI) (infusion reactions [IRs], anaphylaxis, gout flares and cardiovascular [CV] events), laboratory tests, vital signs and physical exam, and incidence of biopsy-confirmed renal rejection.

Study Design:

This is a Phase 4, multi-site, open-label, efficacy and safety study of pegloticase in adult subjects with uncontrolled gout who have undergone kidney transplantation. Twenty subjects will be enrolled.

The study design will include: 1) a Screening Period, lasting up to 35 days; 2) a 24-week treatment period which includes an End-of-Study (Week 24)/Early Termination Visit; 3) a safety follow-up phone/email Visit 30 days after the last infusion; and 4) a 3-month post-treatment follow up visit.

During the Screening Period, eligibility will be confirmed.

Samples for measurement of sUA levels will be collected at the Screening Visit, prior to each infusion, 15-60

minutes after the end of each infusion and at the End-of-Study/Early Termination Visit. Additional samples for sUA levels will be collected at non-infusion Visits at Weeks 21 and 23.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria during Screening will be enrolled at the Day 1 Visit to receive pegloticase 8 mg administered IV every 2 weeks from Day 1 through Week 22, inclusive. During this 24-week treatment phase, subjects who meet the stopping rule (pre-dose sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit, see Stopping Rule section below) or discontinue treatment for any other reason will complete the End-of-Pegloticase-Infusions Visit procedures within 2 weeks and be encouraged to continue to participate in all visits through the end of the study. Subjects will return for regularly scheduled visits and will complete all study visit procedures with the exception of the pegloticase infusion and IR prophylaxis. After the Week 24 Visit (or End-of-Pegloticase-Infusions Visit [if applicable]), subjects should resume regular care for gout per the judgment of the treating physician, including resumption of urate-lowering therapy (ULT) upon pegloticase discontinuation, if appropriate. Subjects will have a 3-Month Follow-up visit to assess clinical status, including sUA levels.

On days of scheduled infusions, pegloticase will be administered after all pre-dose visit assessments have been completed. The date and start and stop time of infusion will be recorded. The date of the first dose of pegloticase is defined as Day 1. All subsequent doses and study visits will be scheduled based on the Day 1 visit date.

It is required that before a subject begins the treatment period, he or she has been taking protocol defined standard gout flare prophylaxis (colchicine at initial dose of 0.3 to 0.6 mg/day if tolerated and low-dose prednisone ≤ 10 mg/day; for subjects already taking chronic corticosteroids, only colchicine 0.3 to 0.6 mg/day should be added. In subjects with eGFR ≤ 30 mL/min/1.73m^2, the dose of colchicine should not be more than 0.3 mg/day. In subjects taking cyclosporine, only low dose prednisone (and not colchicine) should be used for ≥ 1 week before the first infusion. Gout flare prophylaxis should continue for the duration of the 24-week treatment period. Subjects should be monitored closely for symptoms of colchicine excess during the study. Reductions in dose, dose frequency or discontinuation of colchicine are permitted if not tolerated.

For Infusion Reaction (IR) prophylaxis, fexofenadine (60 or 180 mg orally) will be taken the day before each infusion; fexofenadine (60 or 180 mg orally) and acetaminophen (1000 mg orally) will be taken in the morning before each infusion. In addition, methylprednisolone (125 mg IV from Day 1 to Week 10 and 80 mg IV from Week 12 until the end of treatment) is recommended to be administered over an infusion duration between 10 and 30 minutes, immediately prior to each pegloticase infusion. Alternate IV corticosteroid regimen may be substituted for methylprednisolone at the discretion of the Investigator. The dose of fexofenadine should be 60 mg orally in subjects with decreased renal function and 180 mg orally in subjects with normal renal function (eGFR >90 mL/min/1.73m^2).

Serum samples for PK analysis of pegloticase will be collected approximately 15 minutes to 2 hours after the end of infusion on Day 1, prior to the infusion and approximately 15 minutes to 2 hours after the end of infusion at Weeks 2, 6, 14 and 22. An additional PK sample will be collected at the Week 21 non-infusion visit,

End-of-Pegloticase-Infusions Visit (if applicable) and End-of-Study/Early Termination Visit.

Serum samples for evaluation of anti-PEG and anti-uricase immunoglobulin G (IgG) antibodies will be collected prior to the infusion on Day 1 and prior to the infusions at the Weeks 2, 6, 14 and 22. An additional sample will be collected at the End-of-Pegloticase-Infusions Visit (if applicable), End-of-Study/Early Termination Visit and the

3-month follow up visit. In the event of an AE suspected to be an infusion reaction, a sample will be collected at that time or at the subsequent visit for future evaluation of antibodies.

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

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

An overview of the study design is presented in the schematic below.

Screening[1]	Treatment Period[2]	Follow Up[3]
Screen (up to 35 days)	Pegloticase 8 mg IV every 2 weeks	30-days post-last pegloticase infusion and 3 months after End-of-Pegloticase Infusions Visit or Wk 24 End-of-Study/Early Termination Visit
	D1[4] W2 W4 W6 W8 W10 W12 W14 W16 W18 W20 W21[5] W22 W23[5] W24[6]	

1. The Screening Visit can occur up to 35 days prior to the first infusion on Day 1.
2. Subjects will receive pegloticase 8 mg administered IV every 2 weeks from Day 1 through Week 22, inclusive. During this 24-week treatment phase, subjects who meet the sUA-based stopping rule or discontinue treatment for any other reason will complete the End-of-Pegloticase Infusions Visit and will continue the study visits according to the protocol (without treatment).
3. Subjects will receive a phone call/email to assess AEs/SAEs 30 days after the last pegloticase infusion and will be asked to return for a follow up clinic visit 3 months after the End-of-Pegloticase Infusions Visit or Week 24 End-of-Study/Early Termination Visit.
4. Subjects will be enrolled on Day 1 and will receive the first infusion of pegloticase.
5. Non-infusion week collection of serum samples for sUA.
6. The Week 24 Visit is the End-of-Study Visit for pegloticase responders and those that discontinued treatment early. but continued in the study after the End-of-Pegloticase-Infusions Visit. The Week 24 Visit will be the Early Termination Visit for all other subjects that withdrew from the study prior to Week 24.

Abbreviations: D = Day; IV = intravenously; W = Week

Note: The Screening Visit must be completed within 35 days prior to the Day 1 visit. All subsequent study visits must be completed within ± 3 days of the target visit date.

Subject Population:

Subjects eligible for this study will have had a kidney transplant, sUA ≥ 7 mg/dL at Screening and inability to maintain sUA <6 mg/dL on other urate-lowering therapy or intolerant or contraindicated to conventional urate-lowering therapy, and have clinical evidence of tophaceous deposits or have recurrent gout flare or presence of chronic gouty arthritis.

Inclusion Criteria:

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

1. Willing and able to give informed consent;
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study;
3. Adult men or women ≥ 18 years of age;
4. Is a recipient of a de novo kidney from a living or deceased donor and is >1 year post-transplant prior to screening;
5. Is on a stable standard of care immunosuppression therapy for at least 3 months prior to screening;
6. Kidney allograft is functional at entry, based on an estimated GFR (eGFR) ≥ 15 mL/min/1.73m^2;
7. Women of childbearing potential have a negative screening serum pregnancy test and will be required to use a medically approved form of birth control during their participation in the study;
8. Uncontrolled gout, defined as:
9. Hyperuricemia during screening as documented by sUA ≥ 7 mg/dL during Screening and prior to entry into the Treatment Period (Note: the sUA may be repeated up to 3 times during the Screening Period to confirm eligibility), and
10. Inability to maintain sUA <6 mg/dL on other urate-lowering therapy or intolerable side effects or contraindicated with conventional urate-lowering therapy, and
11. At least 1 of the following:
    i. Evidence of tophaceous deposits
    ii. Recurrent gout flares defined as 2 or more flares in the 12 months prior to Screening
    iii. Presence of chronic gouty arthritis; and
12. Able to tolerate low-dose prednisone (<10 mg/day) as part of the required standard gout flare prophylaxis regimen for ≥ 1 week before the first infusion.

Exclusion Criteria:

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

1. Any other organ transplant beside kidney;
2. Any severe infection, unless treated and completely resolved at least 2 weeks prior to Day 1;
3. Chronic or active hepatitis B (HBV) infection;
4. Known history of hepatitis C virus RNA positivity unless treated and viral load is negative;
5. Known history of Human Immunodeficiency Virus (HIV) positivity;
6. Glucose-6-phosphate dehydrogenase (G6PD) deficiency (tested at the Screening Visit);
7. Decompensated congestive heart failure or hospitalization for congestive heart failure within 3 months of the Screening Visit, uncontrolled arrhythmia, treatment for acute coronary syndrome (myocardial infarction or unstable angina), or uncontrolled blood pressure (>160/100 mmHg) at the end of the Screening Period (Day 1 prior to infusion);
8. Pregnant, planning to become pregnant, breastfeeding, planning to impregnate female partner, or not using an effective form of birth control, as determined by the Investigator;
9. Prior treatment with pegloticase, another recombinant uricase (rasburicase), or concomitant therapy with a polyethylene glycol-conjugated drug;
10. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product;
11. Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to Day 1, or plans to take an investigational drug during the study;
12. Currently receiving systemic or radiologic treatment for ongoing cancer;
13. History of malignancy within 5 years other than non-melanoma skin cancer, in situ carcinoma of cervix, early stage renal cell cancer or early stage prostate cancer that has been completely resected >2 years prior to screening;
14. Uncontrolled hyperglycemia with a plasma glucose value >240 mg/dL at Screening that is not subsequently controlled by the end of the Screening Period;
15. Diagnosis of osteomyelitis;
16. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan

and Kelley- Seegmiller syndrome;

17. Unsuitable candidate for the study, based on the opinion of the Investigator (e.g., cognitive impairment), such that participation might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements or complete the study;
18. Currently receiving allopurinol, febuxostat or other urate lowering medications and unable to discontinue medication 7 days prior to Day 1; or
19. Currently receiving probenecid and unable to discontinue medication within 3 days, prior to Day 1.

Dose Regimen/Route of Administration:

Pegloticase:

Pegloticase 8 mg will be administered via IV infusion over ≥ 120 minutes every 2 weeks for a total of 12 infusions from Day 1 through the Week 22 Visit. The date and start and stop time of each infusion will be recorded.

All subjects will receive prophylactic treatment to reduce the risk of acute gout flares beginning ≥ 1 week before the first dose of pegloticase and continuing for the duration of the 24-week treatment period.

Subjects will not be fasting on the day of infusion and will be encouraged to have a snack or normal meal before or after the infusion. Standardized IR prophylaxis consisting of pre-treatment with antihistamines, acetaminophen and corticosteroids will accompany each infusion: fexofenadine (60 or 180 mg orally) will be taken the day before each infusion; fexofenadine (60 or 180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion. In addition, methylprednisolone (125 mg IV from Day 1 to Week 10 and 80 mg IV from Week 12 until the end of treatment) is recommended to be administered over an infusion duration between 10 and 30 minutes, immediately prior to each pegloticase infusion. Alternate IV corticosteroid regimen may be substituted for methylprednisolone at the discretion of the Investigator. The dose of fexofenadine should be 60 mg orally in subjects with decreased renal function and 180 mg orally in subjects with normal renal function (eGFR >90 mL/min/1.73m^2).

Dosage Form and Strength Formulation:

Pegloticase is commercially available in the United States as KRYSTEXXA® and will be supplied as clear, colorless, sterile solution in phosphate-buffered saline (PBS), 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 a 1 mL volume. Pegloticase will be administered as an admixture of 8 mg in 250 mL of 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump. Pegloticase will not be administered as an IV push or bolus.

Duration of Treatment and Follow-up:

Screening: Up to 35 days prior to the Day 1 visit

Treatment Period: Pegloticase for 24 weeks (infusion visits every 2 weeks from Day 1 until the Week 22 Visit).

End-of-Pegloticase-Infusion Visit (if applicable): If the subject discontinues pegloticase treatment prior to the Week 22 infusion, such as due to the sUA stopping rules, the subject will complete this visit within approximately 2 weeks of the last infusion. Subjects will continue in the study.

End-of-Study/Early Termination Visit: Subjects who discontinue treatment during the 24-week treatment period study will be encouraged to continue study participation through the Week 24/End-of-Study Visit. Subjects who discontinue treatment prior to the Week 24 Visit and are not willing to continue in the study will complete the Early Termination Visit.

Safety Follow-up Visit: All subjects will receive a safety follow-up phone call/email approximately 30 days after the last dose of pegloticase to assess if any AEs/SAEs have occurred and will return to the clinic for a follow up visit 3 months after the last pegloticase infusion.

Criteria for Evaluation:

Efficacy will be assessed by sUA levels, tophus resolution, tophus size, urate deposition volume and bone erosion due to gout (determined by DECT), BP, and physician global assessment of gout.

Quality of life will be assessed using the Health Assessment Questionnaire - Disability Index (HAQ-DI),

Health Assessment Questionnaire pain scale (HAQ pain scale) [redacted]

The PK of pegloticase and evaluation of anti-PEG and anti-uricase IgG antibodies will be assessed at specified time points.

Safety assessments will include monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations, and monitoring of hematology and blood chemistry and acute renal rejection.

Hand Held Uric Acid Measurement Device:

Devices may be provided to measure subject uric acid levels in real time.

Stopping Rules:

Individual Subject Stopping Rule based on sUA levels:

During the study, all subjects with pre-infusion sUA levels >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will be discontinued from pegloticase treatment.

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 secondary endpoints are:

- The proportion of 5 mg/dL responders during Month 6 (Weeks 20, 21, 22, 23 and 24), defined as subjects achieving and maintaining sUA <5 mg/dL for at least 80% of the time during Month 6;
- The change from baseline in mean HAQ pain score to Week 24; and
- The change from baseline in mean HAQ-DI score to Week 24.

[redacted]

[redacted]

Pharmacokinetic and Anti-drug Antibody Endpoints:

- Serum concentrations of pegloticase; and
- Profile of anti-PEG and anti-uricase IgG antibodies.

Safety Endpoints:

The safety endpoints include the following:

- Overall AE/SAE profile;
  - Incidences of AESI: IRs, anaphylaxis, gout flares, cardiovascular events;
- Laboratory tests;
- Vital signs and physical examination; and
- Incidence of renal rejection (biopsy proven).

Statistical Analysis of Efficacy Parameters

The efficacy analysis will be performed using the modified intention-to-treat (mITT) population, defined as all enrolled subjects who received at least 1 dose of pegloticase. The proportion of Month 6 responders will be summarized, along with a 95% confidence interval (CI) for the proportion. The proportion of 5 mg/dL responders during Month 6 will be analyzed similarly.

A subject will be declared a non-responder if the subject had sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit through Week 24 (for the primary endpoint) and through Week 14 (for exploratory endpoints). In addition, a subject who withdraws from study treatment for any reason after the first dose of pegloticase and prior to Month 6 (for the primary endpoint) or Month 3 (for exploratory endpoints) will beconsidered a non-responder if sUA values are not collected at the planned time points.

The proportion of subjects with resolution of ≥ 1 tophus (100% decrease in the area of at least 1 tophus) at Week 24 will be summarized along with the corresponding 95% CI. HAQ scores (Disability Index [DI], pain, and health), sUA, urate volume, tophi size, bone erosion, SBP, DBP, MAP, physician global assessment, eGFR, and UACR will be summarized at each visit with descriptive statistics. Changes from baseline will be summarized along with 95% CIs.

Special consideration may be given to subjects who discontinue the study or miss visits due to reasons related to the COVID-19 pandemic.

Sample Size Estimate:

A sample size of 20 subjects is planned for this study. The primary efficacy endpoint, the proportion of subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6, will be demonstrated to be statistically greater than 43.5% (proportion of responders during Month 6 in Phase 3 studies), if at least 14/20 (70%) responders are observed. In that case, the lower bound of a 95% confidence interval for the proportion of responders will be about 46%.

2.1 Schedule of Assessments

Study Procedure/ Assessment	Screening	Treatment Period[2] Day 1 through Week 24													End-of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-Study/ Early Termination	Safety Follow-up Phone/ Email Visit	Post-Treatment Follow-Up[4]
			Week (±3 d)												Within 2 weeks following final infusion if prior to Wk 22	Wk 24 (±3 d)	30 days after last pegloticase infusion (±3 d)	3 months
	Screening Visit[1]	Day 1	2	4	6	8	10	12	14	16	18	20	21	22	23				
Informed consent	X																		
Demographic data	X																		
Inclusion/exclusion criteria	X	X																	
Medical/surgical history[5]	X																		
Medication/ substance use history[6]	X																		
Physical examination[7]	X	X		X		X		X		X		X				X	X		X
Vital signs, height, and weight[8]	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X		X
[redacted]		■			■			■			■					■	■		
Electrocardiogram[9]	X																		
AE/SAE Assessment[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■
HAQ-DI, HAQ Pain Scale[redacted]	X	X			X				X			X				X	X		X

Study Procedure/ Assessment	Screening	Treatment Period[2] Day 1 through Week 24													End-of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-Study/ Early Termination	Safety Follow-up Phone/ Email Visit	Post-Treatment Follow-Up[4]
			Week (±3 d)															
	Screening Visit[1]	Day 1	2	4	6	8	10	12	14	16	18	20	21	22	23	Within 2 weeks following final infusion if prior to Wk 22	Wk 24 (±3 d)	30 days after last pegloticase infusion (±3 d)	3 months
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■
[redacted]	■	■			■				■			■				■	■		■
[redacted]	■								■							■	■		
[redacted]	■	■							■							■	■		■
Gout prophylaxis Rxs filled[13]		Rxs filled as needed																	
Fexofenadine Rx filled[14]		Rxs filled as needed																	
Infusion reaction prophylaxis[15]		X	X	X	X	X	X	X	X	X	X	X		X					
IR prophylaxis compliance (Yes/No)		X	X	X	X	X	X	X	X	X	X	X		X					
Gout flare prophylaxis compliance (Yes/No)		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					
Pegloticase PK sampling[16]		X	X		X				X				X	X		X	X		
sUA[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Blood UA by hand held device(if devices are provided) [17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Study Procedure/ Assessment	Screening	Treatment Period[2] Day 1 through Week 24													End-of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-Study/ Early Termination	Safety Follow-up Phone/ Email Visit	Post-Treatment Follow-Up[4]
			Week (±3 d)															
	Screening Visit[1]	Day 1	2	4	6	8	10	12	14	16	18	20	21	22	23	Within 2 weeks following final infusion if prior to Wk 22	Wk 24 (±3 d)	30 days after last pegloticase infusion (±3 d)	3 months
Hematology	X	X	X		X				X					X		X	X		X
Clinical chemistry	X	X	X		X				X					X		X	X		X
Blood and Urine Collection for Allantoin and Urine Creatinine[22]		X	X	X	X	X	X		X		X			X		X	X		X
Spot urine collection for UACR	X	X	X		X				X					X		X	X		X
Samples for Antibody testing[18]		X	X		X				X					X		X	X		X
HBV Serology	X																		
Sample for G6PD	X																		
Pregnancy test[19]	X	X		X		X		X		X		X				X	X		
Blood Biomarker sampling[20]	X			X					X							X	X		
Principal Investigator assessment of subject clinical status and treatment goals[21]	X															X	X		

Abbreviations: AE = adverse event; d = day(s); DECT = dual-energy computed tomography; G6PD = glucose-6-phosphate dehydrogenase; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBV = hepatitis B virus; IR = infusion reaction; PK = pharmacokinetic; Rx = prescription; SAE = serious adverse event; sUA = serum uric acid; UACR= Urinary Albumin Creatinine Ratio; V = Visit; wk(s) = week(s)

Footnotes:

1. The Screening Visit can occur up to 35 days prior to the Day 1 Visit.
2. Subjects will be enrolled at the Day 1 Visit to receive pegloticase 8 mg administered IV every 2 weeks from Day 1 through Week 22, inclusive. During this 24-week treatment phase, subjects who meet the sUA based stopping rule or discontinue treatment for any other reason will complete the End-of-Pegloticase-Infusions Visit procedures within 2 weeks and be encouraged to continue to participate in all visits through the end of the study. Subjects will return for regularly scheduled visits and will complete all study visit procedures with the exception of the pegloticase infusion and IR prophylaxis. After the Week 24 Visit (or End-of-Pegloticase-Infusions Visit [if applicable]), subjects should resume regular care for gout per the judgment of the treating physician, including resumption of urate-lowering therapy (ULT) upon pegloticase discontinuation, if appropriate. Subjects will have a 3-month Follow-up visit to assess clinical status, including sUA levels.
3. Subjects who end treatment due to the stopping rules or other reasons should complete the End-of-Pegloticase-Infusions Visit within 2 weeks of the last infusion. Subjects should remain on study. See Section 9.3.3.1.1 for details on visits and procedures.
4. All subjects will have a follow up visit 3 months following the End-of-Pegloticase Infusions Visit or Week 24/End-of-Study/Early Termination Visit. If the subject ends treatment early but remains in the study and the 3-month Post Treatment Follow-up Visit occurs prior to Week 24, the 3-month Post Treatment Follow-up Visit will be adjusted accordingly based on the timing of the last treatment.
5. The Investigator or designee will collect a complete gout history and other relevant medical/surgical history.
6. Medication history (i.e., prior medications) will include gout medications, starting at the time of diagnosis and up to (but not including) the Day 1 Visit; substance use history; and all other medications up to (but not including) the Day 1 Visit. Prior concomitant medications (not including gout medications) will be collected for 1 year prior to Screening.
7. A complete physical examination will be performed at the Screening Visit and will include assessments of head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, extremities, neurological status and musculoskeletal system, and for presence of tophi, as well as gout history and symptom severity. A targeted physical examination (for joint and skin evaluation and assessment of AEs) will be conducted based on potential risk for or occurrence of AEs at Day 1, and prior to administration of infusion at Weeks 4, 8, 12, 16, and 20, the End-of-Pegloticase-Infusions Visit (if applicable), Week 24/End-of-Study/Early Termination Visit and 3-month Post-Treatment Follow Up Visit; at a minimum this should include heart, lungs, and abdomen. Clinically significant findings from the targeted physical examinations will be recorded as AEs.
8. BP, respiratory rate, temperature, and heart rate will be measured at every visit, BEFORE study drug infusion and any scheduled blood draws. Heart rate and BP measurements should be taken after the subject has been in a sitting position and in a rested and calm state with proper positioning including back support, feet flat on the floor, for at least 5 minutes (See Section 9.5.4.4 for detailed BP measurement procedures). 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 the same arm is to be used consistently at each study visit. The Korotkoff phase V will be used to determine DBP. The cuff deflation rate should be 2 mmHg per second. [redacted]

[redacted] MAP will be calculated from SBP and DBP as MAP = 1/3 * SBP + 2/3 * DBP. Weight should be measured in kilograms or pounds without shoes and recorded at the Screening Visit, prior to pegloticase infusion on Day 1, at the Week 8 and 16 Visits, the non-infusion End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit, and the 3-month Post-Treatment Follow-up Visit. Height will be collected at the Screening Visit only.

9. Electrocardiogram should be completed during Screening. The electrocardiogram is read at the site. If a subject experiences an AE suspected to be an IR, a 12-lead ECG will also be performed.
10. AEs/SAEs will be collected from the time of signature of the ICF until the 3-month Post-Treatment Follow-up Visit. For each AE, the Investigator will be asked to record if the event was possibly an infusion reaction or anaphylaxis and if so, will be prompted to complete additional eCRFs.
11. [redacted]
13. Subjects are required to take at least one protocol standard gout flare prophylaxis (i.e., colchicine initial dose 0.3-0.6 mg/day and low-dose prednisone | ≤ 10 mg/day); for subjects already taking low dose corticosteroids, colchicine 0.3-0.6 mg/day should be added. In subjects with eGFR ≤ 30 mL/min/1.73m2, the dose of colchicine should not be more than 0.3 mg/day. In subjects taking cyclosporine, only low dose prednisone (and no colchicine) should be used for ≥ 1 week before the first infusion. Gout flare prophylaxis should continue for the duration of the 24-week treatment period. Subjects should be monitored closely for symptoms of colchicine excess during the study. Reductions in dose, dose frequency or discontinuation of colchicine are permitted if not tolerated.
14. For IR prophylaxis, fexofenadine (60 - 180 mg orally) will be taken the night before each infusion.
15. IR prophylaxis includes fexofenadine administered the day before each infusion; fexofenadine and acetaminophen (1000 mg orally) administered on the morning of each infusion. In addition, methylprednisolone (125 mg IV from Day 1 to Week 10 and 80 mg IV from Week 12 until the end of treatment) is recommended to be administered over an infusion duration between 10 and 30 minutes, immediately prior to each pegloticase infusion. Alternate IV corticosteroid regimen may be substituted for methylprednisolone at the discretion of the Investigator. The dose of fexofenadine should be 60 mg orally in subjects with decreased renal function and 180 mg orally in subjects with normal renal function (eGFR >90 mL/min/1.73m^2).

16. For all subjects, serum samples for pegloticase PK analysis will be collected approximately 15 minutes to 2 hours after the end of infusion on Day 1; prior to infusion and approximately 15 minutes to 2 hours after the end of the infusion at Weeks 2, 6, 14, and 22. An additional PK sample will be collected at Week 21, the End-of-Pegloticase-Infusions Visit (if applicable) and the Week 24/End-of-Study/Early Termination Visit.
17. Serum samples for measurement of sUA levels will be collected at the Screening Visit, within 48 hours prior to each pegloticase infusion and after the end of each pegloticase infusion prior to discharge from the site. Additional serum samples for sUA levels will be collected at non-infusion Visits at Weeks 21 and 23 and the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit, and the 3-month Follow-up Visit. For subjects whose previous visit's pre-infusion sUA value is > 6 mg/dL, two separate samples/tubes of blood should be collected within 48 hours prior to the pegloticase infusion (except on Day 1 when only 1 pre-infusion sample is required for the central laboratory); one sample/tube will be assessed by the site's local laboratory for pre-infusion sUA results for on-study subject management. If a local laboratory sample is drawn (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit. The second sample/tube will be sent to the central laboratory for analysis and recording in the database. Hand held uric acid measurement devices may be provided to measure subject uric acid levels in real time. If hand held devices are provided, blood uric acid levels prior to each pegloticase infusion and after the end of each pegloticase infusion prior to discharge from the site at the selected visits will recorded in database, but NOT to be used to manage pegloticase treatment. See the Laboratory Manual for instructions for alternate scenarios.
18. Serum samples for evaluation of anti-PEG antibodies and anti-uricase IgG antibodies will be collected prior to the infusion on Day 1 and at Weeks 2, 6, 14, and 22. An additional sample will be collected at each of the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit, and the 3-month Study Follow Up Visit. In the event of an AE suspected to be an infusion reaction, a serum sample will be collected in a serum separating tube at that time or at the subsequent visit for future evaluation of pegloticase antibodies.
19. For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit and at the Week 24/End-of-Study/Early Termination Visit. A urine pregnancy test will be performed at all other indicated visits.
20. Blood samples will be collected from consenting subjects for serum and for peripheral blood mononuclear cell (PBMC) isolation for potential analysis of inflammatory biomarkers, markers related transplant outcome, gout or gout co-morbidities in response to pegloticase or other potential treatment for gout. Subjects who consent to the optional blood draw for analysis of biomarkers but screen fail will be requested to return 24 weeks +/- 4 weeks for an additional blood sample. Adverse events, concomitant medications and vital signs will also be collected as an unscheduled visit at that time.
21. The Investigator will review the clinical status and individual subject treatment goals at Screening, the End-of-Pegloticase-Infusions Visit (if applicable) and the Week 24/End-of-Study/Early Termination Visit.
22. Blood and urine samples will be collected prior to pegloticase infusion on Day 1 and at the Week 2, 4, 6, 8, 10, 14, 18, and 22 Visits, the End of Pegloticase Infusions Visit (if applicable), the Week 24/End of Study/Early Termination Visit, and the 3 month Post Treatment Follow-up Visit. In addition, blood and urine samples will be collected after the end of pegloticase infusions prior to discharge from the site at on Day 1, Week 2, 6, 14 and 22 Visits. The urine collected is aliquoted into separate tubes, one of which will be used by the central lab for analysis of creatinine in order to calculate urine allantoin/creatinine ratio.

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
AZA	azathioprine
BP	blood pressure
cDNA	complementary deoxyribonucleic acid
CFR	Code of Federal Regulations
CI	confidence interval
C	creatinine
CR	complete response
CV	cardiovascular
DBP	diastolic blood pressure
DECT	dual-energy computed tomography
DI	Disability Index
dL	deciliter
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAAN	Food Allergy and Anaphylaxis Network
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
HBV	hepatitis B virus
HEENT	head, eyes, ears, nose, and throat
Hg	mercury
HIPPA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HIV	Human Immunodeficiency Virus
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IND	Investigational New Drug
IR	infusion reaction
IRB	Institutional Review Board
IV	intravenous(ly)
kDa	kilodalton
L	liter
µm	micrometer
µmol	micromole
MAP	mean arterial pressure
MDRD	Modification of Diet in Renal Disease (equation)
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mITT	modified intention-to-treat
mL	milliliter
mm	millimeter
mPEG	methoxy- poly(ethylene glycol)
MR	marked response
mRNA	messenger ribonucleic acid
MTX	methotrexate
NIAID	National Institute of Allergy and Infectious Diseases
ODA	Orphan Drug Act
PBMC	peripheral blood mononuclear cell
PBS	phosphate-buffered saline
PD	progressive disease
PEG	poly(ethylene glycol)

Abbreviation	Definition
PI	Principal Investigator
PK	pharmacokinetic(s)
PO	oral
PR	partial response
pUA	plasma uric acid
QoL	Quality of Life
RCT	randomized controlled trial
RCTC	Rheumatology Common Toxicity Criteria
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SBP	systolic blood pressure
Scr	serum creatinine
SD	stable disease
sUA	serum uric acid
TFG	treatment failure gout
UA	uric acid
UACR	urine albumin-to-creatinine ratio
UE	unable to evaluate
ULT	urate lowering therapy
USP	United States Pharmacopeia
VAS	visual analog scale

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

5.2 Ethical Conduct of the Study

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

5.3 Subject Information and Consent

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

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

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

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

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

5.4 Compensation for Health Damage of Subjects/Insurance

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

5.5 Confidentiality

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

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

If the results of the study are published, the subject's identity will remain confidential. The Investigator will maintain a list to enable subjects to be identified.

The Sponsor will ensure that the use and disclosure of protected health information obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (e.g., Health Insurance Portability and Accountability Act [HIPAA]).

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Sponsor of this study is Horizon Therapeutics Ireland DAC (Horizon). Horizon personnel will serve as the Medical Monitor and the Sponsor's regulatory representative (see 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 requi17.1red. The Sponsor will be responsible for timely reporting of SAEs and any other new pertinent safety information to all Investigators, as required.

The study will be conducted at approximately 15 study centers in the United States. Prior to initiation of the study, each Investigator will provide the Sponsor or its designee with a fully executed and signed Food and Drug Administration (FDA) Form 1572 and a Financial Disclosure Form. Financial Disclosure Forms will also be completed by all sub-investigators listed on the Form 1572. It is the responsibility of the Investigators or sub-investigators to advise the Sponsor of any change in the relevant financial interests that occur during the study and the 1-year period following its completion.

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

Table 6.1 Table of Non-Sponsor Study Responsibilities

Study Responsibility	Organization
Clinical drug supply and distribution	[redacted]
Central safety laboratory	[redacted]
Data Management	[redacted]
Statistics	[redacted]
Adjudication Committee	[redacted]
Central imaging vendor	[redacted]

7 INTRODUCTION

7.1 Background

7.1.1 Gout

Gout affects approximately 4% of the United States population, is the most common form of inflammatory arthritis in men, and is associated with decreased quality of life (Saag and Choi, 2006; Singh and Strand, 2008; Zhu et al., 2011; Sattui et al., 2014). The frequency of gout is increasing worldwide, with prevalence rates estimated to be as high as 7% in older men (Mikuls et al., 2005; Saag and Choi, 2006; Roddy and Doherty, 2010). While the exact prevalence is unknown, as many as 200,000 persons in the United States experience chronic symptoms of gout, which is sometimes referred to as chronic refractory gout, despite trials of oral urate-lowering therapy. This condition 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.

Gout and hyperuricemia (defined as a serum uric acid level >6.0 mg/dL [Kidney Disease: Improving Global Outcomes {KDIGO} Guidelines, 2009]) are major problems in the population of kidney transplant recipients. The prevalence rate of 13.1% for gout in the kidney transplant recipient population is approximately 12-fold higher than the prevalence rate for gout in the general non transplanted US population (p <0.0001) (Brigham et al., 2018). Potential contributors to greater disease severity in gout patients with kidney transplants are reduced urate excretion due to renal impairment and reduced utilization of key urate lowering therapies leading to poorer gout control. It is also possible that increased gout severity leads to greater risk of renal failure and hence, the need for transplantation, consistent with evidence of hyperuricemia and gout as risk factors for chronic kidney disease and end-stage renal disease (Radeck et al., 2018). Managing gout in kidney transplant recipients is challenging as it is complicated by serious underlying diseases and by drug regimens needed to treat these conditions and to prevent graft rejection (Stamp et al., 2005). Some immunosuppressive drugs increase uric acid and many conventional urate lowering therapies are potentially contraindicated in kidney transplant recipients.

7.1.2 Pegloticase

[redacted]

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

In the Phase 3 pivotal studies, deaths, AEs, SAEs, as well as 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 vs. placebo during Months 4-6. Despite use of prophylactic medications against hypersensitivity including administration of corticosteroids, antihistamine, and acetaminophen in advance of each pegloticase infusion, IRs were seen in 22/85 (26%) of subjects receiving the 8 mg 2 week regimen. There was no specified definition of anaphylaxis in the Phase 3 protocols, and there were no investigator-reported events of anaphylaxis in the Phase 3 studies with pegloticase.

However, in a post-hoc review applying the National Institute of Allergy and Infectious Diseases/ Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria (Sampson et al., 2006), it was determined that across the Phase 2 and Phase 3 program, anaphylaxis occurred in 6.5% of subjects treated with pegloticase dosed every 2 weeks. Anaphylaxis generally occurred within 2 hours after treatment. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. All of these events had relatively rapid resolution with the cessation of infusion.

In a post-hoc analysis, the apparent role of immunogenicity in both loss of urate lowering effect and incidence of 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 greater than 6 mg/dL. Retrospective analyses showed that the loss of urate-lowering efficacy, as reflected by sUA of greater than 6 mg/dL, preceded a patient's first IR, whenever it occurred, in 20 (91%) of 22 subjects treated with pegloticase every 2 weeks.

Therefore, discontinuation of pegloticase therapy in subjects who lose urate-lowering response offers a valuable approach for mitigating the risk of IR. A post-hoc analysis of the biweekly pegloticase dosing group in the randomized controlled trials (RCTs) illustrated the impact of several possible stopping rules based on sUA levels. A stopping rule based on 2 consecutive pre-infusion sUA

measurements of greater than 6 mg/dL would have significantly reduced the risk of IR (from 26% to 8%), while having little effect on the treatment response rate (from 42% to 41%) (Keenan et al., 2019). Early post-approval safety surveillance in the US using the stopping rules demonstrated a 69% reduction in the rate of IRs compared with the IR rate recorded during the RCTs (Malamet et al., 2013).

Reducing anti-drug antibodies (ADA) with concomitant administration of the immunomodulatory agent methotrexate (MTX) has been shown to be useful with other infused products that lead to immunogenicity, such as infliximab, in the setting of rheumatoid arthritis treatment. In a recent, prospective, proof-of-concept case series, nine patients with refractory tophaceous gout were pre-treated with MTX prior to co-administration of MTX with KRYSTEXXA. All nine patients were responders as defined by maintaining a serum uric acid at goal of <6 mg/dL for greater than 80% of the observation period, which ranged from 4.5 to

9 months on therapy. No unexpected adverse effects were reported with this coadministration (Botson and Peterson, 2018).

Inherent in organ transplantation is the need for immunosuppression to maintain the viability of the transplant, and prevent rejection. There are no formal clinical trials of uricases, including pegloticase, in kidney transplant recipients with gout, although pegloticase has been used successfully in a small number of transplant recipients. Hershfield et al. (2014) reported a trial of pegloticase administered as 8 mg intravenously (IV) every three weeks for up to 5 infusions to 30 patients, including 7 kidney transplant recipients, with refractory gout who were receiving immunosuppression with various combinations of mycophenolate mofetil, cyclosporine, tacrolimus, and azathioprine (AZA). Five of the 7 transplant recipients responded well to pegloticase, and only 1 of 7 developed antibodies to pegloticase, compared to 9 of

20 pegloticase-naïve non-transplant recipients who were not on immunosuppressives. Of the two transplant recipients who did not respond well to pegloticase, one discontinued at the time of the second infusion with an unrelated SAE (duodenal ulcer which caused loss of the pancreatic graft), and the other discontinued after the third infusion with an unrelated SAE (myocardial infarction); the subject with the myocardial infarction was also the one transplant recipient who developed anti-pegloticase antibodies.

7.1.2.1 Physiochemical Properties

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

7.1.2.2 Safety Pharmacology

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

7.1.2.3 Non-clinical Pharmacokinetics

[redacted]

[redacted]

[redacted]

7.1.2.4 Clinical Pharmacokinetics

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.1.2.5 Risks of Pegloticase

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

[redacted]

7.2 Rationale for this Study

During the pre-marketing Phase 3 studies for pegloticase, subjects with organ transplant were excluded from participation; however, subjects with renal impairment were included, and showed comparable safety and efficacy as the general study population. Kidney transplant recipients with uncontrolled gout have the potential to benefit from the ability of pegloticase to rapidly deplete urate deposits, even when urate excretion is impaired. In addition, immunosuppressive agents to prevent rejections have the potential to thwart the formation of ADA against pegloticase, thereby preserving its effectiveness and decreasing the risk of infusion reactions.

This study will test safety and effectiveness of pegloticase 8 mg administered intravenously every 2 weeks in kidney transplant subjects with chronic gout refractory to conventional urate lowering therapy (ULT). Prospective use of sUA stopping rules, with pegloticase treatment cessation (but study continuation) when a subject has a pre-infusion sUA level >6 mg/dL on two consecutive study visits, will also help confirm the value of this approach to reduce IR risk.

7.3 Rationale for Dose Selection

[redacted]

8 STUDY OBJECTIVES

The overall objective of the study is to assess the efficacy and safety of pegloticase in kidney transplant subjects with uncontrolled gout refractory to conventional urate lowering therapy.

Primary Objective:

To evaluate the effect of pegloticase on the response rate of sustained serum uric acid (sUA) reduction to sUA <6 mg/dL during Month 6 of treatment.

Secondary Objectives:

- To evaluate the effect of pegloticase on the response rate of sustained serum uric acid reduction to sUA <5 mg/dL during Month 6 of treatment;
- To evaluate the effect of pegloticase on pain assessed by the Health Assessment Questionnaire (HAQ) pain score; and
- To evaluate the effect of pegloticase on disability assessed by the Health Assessment Questionnaire - Disability Index (HAQ-DI) score.

Exploratory Objectives:

- [redacted]
- To evaluate the pharmacokinetics (PK) of pegloticase and the profile of anti-methoxy-poly(ethylene glycol) (PEG) and anti-uricase IgG antibodies; and
- To evaluate the safety and efficacy 3 months after the end of treatment with pegloticase.

Safety and Tolerability Objectives:

To assess the overall adverse event (AE)/serious AE (SAE) profile including AEs of special interest (AESI) (infusion reactions [IRs], anaphylaxis, gout flares and cardiovascular [CV] events), laboratory tests, vital signs and physical exam, and incidence of biopsy confirmed renal rejection.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 4, multi-site, open-label, efficacy and safety study of pegloticase in adult subjects with uncontrolled gout who have undergone kidney transplantation. Twenty subjects will be enrolled.

The study design will include: 1) a Screening Period, lasting up to 35 days; 2) a 24-week treatment period which includes an End-of-Study (Week 24)/Early Termination Visit; 3) a safety follow-up phone/email Visit 30 days after the last infusion; and 4) a 3-month post-treatment follow up visit.

During the Screening Period, eligibility will be confirmed.

Samples for measurement of sUA levels will be collected at the Screening Visit, prior to each infusion, 15-60 minutes after the end of each infusion and at the Week 24/End-of-Study/Early Termination Visit. Additional samples for sUA levels will be collected at non-infusion Visits at Weeks 21 and 23.

Subjects who meet all of the inclusion criteria and none of exclusion criteria during Screening will be enrolled at the Day 1 Visit to receive pegloticase 8 mg administered IV every 2 weeks from Day 1 through Week 22, inclusive. During this 24-week treatment phase, subjects who meet the stopping rule (based on elevated sUA levels, see Stopping Rule in Section 9.5.7.2) or discontinue treatment for any other reason will complete the End-of-Pegloticase-Infusions Visit procedures within 2 weeks and be encouraged to continue to participate in all visits through the end of the study. Subjects will return for regularly scheduled visits and will complete all study visit procedures with the exception of the pegloticase infusion and IR prophylaxis. After the Week 24/End-of-Study/Early Termination Visit (or End-of-Pegloticase-Infusions Visit [if applicable]), subjects should resume regular care for gout per the judgment of the treating physician, including resumption of ULT upon pegloticase discontinuation, if appropriate.

Subjects will have a 3-month Follow-up visit to assess clinical status, including sUA levels.

On days of scheduled infusions, pegloticase will be administered after all pre-dose study visit assessments have been completed. The date and start and stop times of infusion will be recorded. The date of the first dose of pegloticase is defined as Day 1. All subsequent doses and study visits will be scheduled based on the Day 1 Visit date.

It is required that before a subject begins the treatment period, he or she has been taking protocol defined standard gout flare prophylaxis (i.e., colchicine initial dose 0.3 to 0.6 mg/day if tolerated and low-dose prednisone $\leq$ 10 mg/day); for subjects already taking chronic corticosteroids, colchicine 0.3 to 0.6 mg/day should be added. In subjects with eGFR $\leq$ 30 mL/min/1.73m^2, the dose of colchicine should not be more than 0.3 mg/day. In subjects taking cyclosporine, only low dose prednisone (and not colchicine) should be used for $\geq$ 1 week before the first infusion. Gout flare prophylaxis should continue for the duration of the 24-week treatment period. Subjects should be monitored closely for

symptoms of colchicine excess during the study. Reductions in dose, dose frequency or discontinuation of colchicine are permitted if not tolerated.

For IR prophylaxis, fexofenadine (60 or 180 mg orally) will be taken the day before each infusion; fexofenadine (60 or 180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion. In addition, methylprednisolone (125 mg IV from Day 1 to Week 10 and 80 mg IV from Week 12 until the end of treatment) is recommended to be administered over an infusion duration between 10 and 30 minutes, immediately prior to each pegloticase infusion. Alternate IV corticosteroid regimen may be substituted for methylprednisolone at the discretion of the Investigator. The dose of fexofenadine should be 60 mg orally unless in subjects with decreased renal function and 180 mg orally in subjects with normal renal function (eGFR>90 mL /min/1.73m^2).

Serum samples for PK analysis of pegloticase will be collected approximately 15 minutes to 2 hours after the end of infusion on Day 1, prior to the infusion and approximately 15 minutes to 2 hours after the end of infusion at Weeks 2, 6, 14 and 22. An additional PK sample will be collected at the Week 21 Visit, End-of-Pegloticase-Infusions Visit (if applicable) and Week 24/End of Study/Early Termination Visit.

Serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies will be collected prior to the infusion on Day 1 and prior to the infusions at the Weeks 2, 6, 14 and 22. An additional sample will be collected at each of the End-of-Pegloticase-Infusions Visit (if applicable),

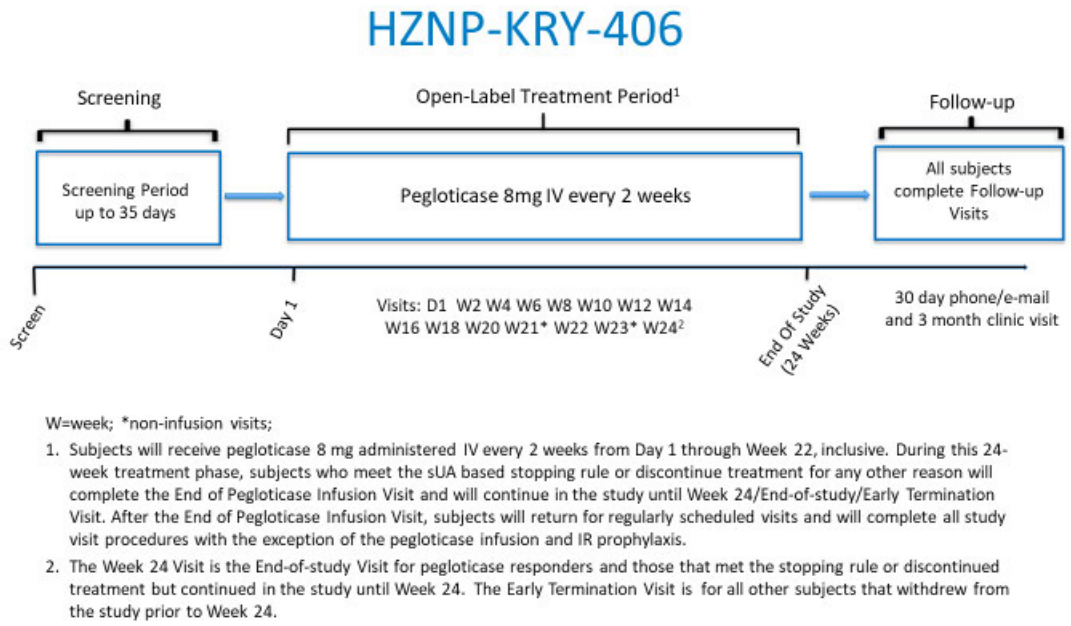
Week 24/End-of-Study /Early Termination Visit and the 3-month follow up visit. In the event of an AE suspected to be an IR, a sample will be collected at that time or at the subsequent visit for future evaluation of ADAs.

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 acute renal rejection, will be performed.

An independent external adjudication committee will review reported events of IRs, major CV events and anaphylaxis.

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

Figure 9.1 Schematic of Study Design



W=week; *non-infusion visits;

1. Subjects will receive pegloticase 8 mg administered IV every 2 weeks from Day 1 through Week 22, inclusive. During this 24-week treatment phase, subjects who meet the sUA based stopping rule or discontinue treatment for any other reason will complete the End of Pegloticase Infusion Visit and will continue in the study until Week 24/End-of-study/Early Termination Visit. After the End of Pegloticase Infusion Visit, subjects will return for regularly scheduled visits and will complete all study visit procedures with the exception of the pegloticase infusion and IR prophylaxis.
2. The Week 24 Visit is the End-of-study Visit for pegloticase responders and those that met the stopping rule or discontinued treatment but continued in the study until Week 24. The Early Termination Visit is for all other subjects that withdrew from the study prior to Week 24.

9.2 Discussion of Study Design

This is a Phase 4, multi-site, open-label, single arm study to assess efficacy and safety of pegloticase in adult subjects with uncontrolled gout who have undergone kidney transplantation.

During the pre-marketing Phase 3 studies for pegloticase, subjects with organ transplant were excluded from participation; however, subjects with renal impairment were included, and showed comparable safety and efficacy as the general study population. Kidney transplant recipients with uncontrolled gout have the potential to benefit from the ability of pegloticase to rapidly deplete urate deposits, even when urate excretion is impaired. In addition, immunosuppressive agents to prevent rejections have the potential to thwart the formation of ADA against pegloticase, thereby preserving its effectiveness and decreasing the risk of infusion reactions.

This study will test safety and effectiveness of pegloticase (administered 8 mg via IV infusion every 2 weeks, consistent with the current pegloticase prescribing information) in kidney transplant subjects with chronic gout refractory to conventional urate lowering therapy.

Prospective use of sUA stopping rules, with pegloticase treatment cessation (but study continuation) when a subject has an pre-infusion an sUA level >6 mg/dL on two consecutive study visits, will also help confirm the value of this approach to reduce IR risk.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

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

1. Willing and able to give informed consent;
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study;
3. Adult men or women ≥18 years of age;
4. Is a recipient of a de novo kidney from a living or deceased donor and is >1 year post-transplant prior to screening;
5. Is on a stable standard of care immunosuppression therapy for at least 3 months prior to screening;
6. Kidney allograft is functional at entry, based on an estimated GFR (eGFR) ≥ 15 mL/min/1.73m$^{2;}$
7. Women of childbearing potential have a negative screening serum pregnancy test and will be required to use a medically approved form of birth control during their participation in the study;
8. Uncontrolled gout, defined as:
   A. Hyperuricemia during screening as documented by sUA ≥ 7 mg/dL during Screening and prior to entry into the Treatment Period (Note: the sUA may be repeated up to 3 times during the Screening Period to confirm eligibility); and
   B. Inability to maintain sUA <6 mg/dL on other urate-lowering therapy or intolerable side effects or contraindicated with conventional urate-lowering therapy; and
   C. At least 1 of the following:
      i. Evidence of tophaceous deposits;
      ii. Recurrent gout flares defined as 2 or more flares in the past 12 months prior to Screening;
      iii. Presence of chronic gouty arthritis; and
9. Able to tolerate low-dose prednisone (<10 mg/day) as part of the required standard gout flare prophylaxis regimen for ≥ 1 week before the first infusion.

9.3.2 Exclusion Criteria

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

1. Any other organ transplant beside kidney;
2. Any severe infection, unless treated and completely resolved at least 2 weeks prior to Day 1;
3. Chronic or active hepatitis B (HBV) infection;
4. Known history of hepatitis C virus RNA positivity unless treated and viral load is negative;
5. Known history of Human Immunodeficiency Virus (HIV) positivity;
6. Glucose-6-phosphate dehydrogenase (G6PD) deficiency (tested at the Screening Visit);
7. Decompensated congestive heart failure or hospitalization for congestive heart failure within 3 months of the Screening Visit, uncontrolled arrhythmia, treatment for acute coronary syndrome (myocardial infarction or unstable angina), or uncontrolled blood pressure (>160/100 mmHg) at the end of the Screening Period (Day 1 prior to infusion);
8. 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;
9. Prior treatment with pegloticase, another recombinant uricase (rasburicase), or concomitant therapy with a polyethylene glycol-conjugated drug;
10. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product;
11. Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to Day 1 or plans to take an investigational drug during the study;
12. Currently receiving systemic or radiologic treatment for ongoing cancer;
13. History of malignancy within 5 years other than non-melanoma skin cancer, in situ carcinoma of cervix, early stage renal cell cancer or early stage prostate cancer that has been completed resected >2 years prior to Screening;
14. Uncontrolled hyperglycemia with a plasma glucose value >240 mg/dL at Screening that is not subsequently controlled by the end of the Screening Period;
15. Diagnosis of osteomyelitis;
16. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome;
17. Unsuitable candidate for the study, based on the opinion of the Investigator (e.g., cognitive impairment), such that participation might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements or complete the study;
18. Currently receiving allopurinol, febuxostat or other urate lowering medications and unable to discontinue medication 7 days prior to Day 1; or

19. Currently receiving probenecid and unable to discontinue medication within 3 days, prior to Day 1.

9.3.3 Removal of Subjects From Therapy or Study

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

9.3.3.1 Removal of Subjects From Pegloticase Therapy

In addition to completion of therapy through Week 24, the reason for discontinuation from the therapy should be recorded on the eCRF using 1 of the following categories:

- Lack of Efficacy: (i.e., sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit);
- Adverse Event: The subject experiences an AE that imposes an unacceptable risk to the subject's health (e.g., anaphylactic reaction), or the subject is unwilling to continue therapy because of an AE. Subjects who discontinue treatment 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 (specify reason);
- 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;
- Study Terminated by Sponsor: The Sponsor, IRB, or regulatory agency terminates the study;
- Pregnancy; and
- Death

9.3.3.1.1 Study considerations for subjects ending pegloticase infusions prior to 24 weeks

- All subjects will remain on study through 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 through the end of the study. Subjects are especially encouraged to complete study visits at the study site during key efficacy and safety collections at Weeks 20, 21, 22, 23, and 24 so that sUA labs and other key assessments can be completed. During visits between these key efficacy and safety collection visits, in subjects who have stopped infusions, subjects may complete study visits

in person or via telephone to collect AEs, concomitant medications 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:
  - Infusion reaction prophylaxis;
  - IR prophylaxis compliance;
  - Pegloticase infusion; and
  - Pegloticase PK sampling
- Re-introduction of oral ULTs should not start until after the End of Pegloticase Visit laboratory tests are collected.

Post-Treatment Follow-up:

The intent is to obtain at least 3 months of follow-up on each subject after cessation of pegloticase infusions. If the subject ends treatment early but remains in the study and the 3- month Post Treatment Follow-up Visit occurs prior to Week 24, the 3-month Post Treatment Follow-up Visit will be adjusted accordingly based on the timing of the last treatment.

9.3.3.2 Removal of Subjects From Study

In addition to completion of therapy and designated study visits through Week 24, the reason for discontinuation from the study should be recorded on the eCRF using 1 of the following categories:

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

9.3.4 Replacement Policy

9.3.4.1 Subjects

In general, subjects that prematurely discontinue from the study for any reason will not be replaced. An exception may be made for subjects who are unevaluable due to the impact of the 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 study 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; or
- Poor protocol adherence.

9.3.4.3 Screen Failures

Subjects who do not meet all of the eligibility criteria or withdraw consent between Screening and Day 1 will be considered screen failures. Screen failures may be allowed to rescreen for the study if both the Investigator and Sponsor are in agreement regarding rescreening and if the Investigator determines that they can satisfy all of the eligibility criteria.

Subjects who fail screening but consented to the optional blood draw for biomarker analysis will be requested to return to the site 24 weeks +/- 4 weeks for a second blood sample. Adverse events, concomitant medications, blood samples for hematology and clinical chemistry and vital signs will also be collected as an unscheduled visit at that time.

9.4 Treatments

9.4.1 Treatments Administered

Starting at the Day 1 visit, subjects will receive pegloticase at a dose of 8 mg administered IV every 2 weeks for a total of 12 infusions from Day 1 through the Week 22 Visit.

After the Week 24 Visit, subjects should resume regular care for gout per the judgment of the treating physician, including resumption of ULT upon pegloticase discontinuation, if appropriate. Subjects will have a 3-month Follow-up visit to assess clinical status, including sUA levels.

9.4.1.1 Gout Flare Prophylaxis

It is required that before a subject begins the treatment period, he or she has been taking protocol defined standard gout flare prophylaxis (i.e., colchicine initial dose 0.3-0.6 mg/day if tolerated and low-dose prednisone ≤ 10 mg/day); for subjects already taking low dose corticosteroids, colchicine 0.3-0.6 mg/day should be added. In subjects with eGFR ≤30 mL/min/1.73m^2, the dose of colchicine should not be more than 0.3 mg/day. In subjects taking cyclosporine, only low dose prednisone (and not colchicine) should be used for ≥ 1 week before the first infusion.

Gout flare prophylaxis should continue for the duration of the 24-week treatment period. Subjects should be monitored closely for symptoms of colchicine excess during the study. Reductions in dose, dose frequency or discontinuation of colchicine are permitted if not tolerated.

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

9.4.1.2 Infusion Reaction Prophylaxis

Since IRs can occur with pegloticase, all subjects will receive IR prophylaxis prior to each infusion, consisting of an antihistamine, acetaminophen, and a corticosteroid. To standardize this regimen, subjects will receive fexofenadine (60 or 180 mg orally) the day before each infusion; fexofenadine (60 or 180 mg orally) and acetaminophen (1000 mg orally) the morning of each infusion. In addition, methylprednisolone (125 mg IV from Day 1 to Week 10 and 80 mg IV from Week 12 until the end of treatment) is recommended to be administered over an infusion duration between 10 and 30 minutes, immediately prior to each pegloticase infusion.

Alternate IV corticosteroid regimen may be substituted for methylprednisolone at the discretion of the Investigator. The dose of fexofenadine should be 60 mg orally in subjects with decreased renal function and 180 mg orally in subjects with normal renal function (eGFR

>90 mL/min/1.73m^2). Substitution of the corticosteroid is not allowed. The name, dose, route, date, and time of administration of each prophylactic medication will be recorded in the medical record and in the eCRF. The methylprednisolone used for IR prophylaxis will be supplied by the site. Other IR medications administered prior to each infusion may also be supplied by the site.

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

As a precaution, emergency equipment will be readily available to treat a possible hypersensitivity reaction, and will include drugs that would be used to treat an anaphylactic reaction. Personnel trained in managing IRs and in the use of the emergency equipment will be readily available during and for 1 hour after the infusion. As IRs can occur after the completion of the infusion, subjects will be observed for 1 hour post-infusion.

9.4.2 Identity of Investigational Products

9.4.2.1 Pegloticase

Pegloticase is a clear, colorless, sterile solution in phosphate-buffered saline (PBS) intended for IV infusion after dilution. Each mL of pegloticase contains 8 mg of uricase protein conjugated to 24 mg of 10 kDa monomethoxypoly(ethylene glycol). Excipients include disodium hydrogen phosphate dihydrate, sodium chloride, sodium dihydrogen phosphate dihydrate, and water for injection.

9.4.3 Labeling

Pegloticase is commercially available in the United States as KRYSTEXXA and will be supplied by PCI Pharma Services packaged in sterile, single-use 2-mL glass vials with a Teflon®-coated (latex-free) rubber injection stopper to deliver pegloticase as 8 mg of uricase protein in 1 mL volume. An ancillary label will be fixed to the vial and carton that identifies the study, allows subject information to be entered, and contains the investigational use caution statement according to the FDA Title 21 CFR Part 312 requirements. Each vial label will have a unique number.

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).

9.4.5 Drug Accountability

Clinical supplies will be dispensed only in accordance with the protocol. Accurate records of the clinical supplies received, the amount dispensed for each subject, and the amount remaining at the conclusion of the study will be maintained.

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

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

9.4.6 Study Drug Administration and Timing of Dose for each Subject

9.4.6.1 Description of Clinical Supplies

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

9.4.6.2 Determination of Dose Volume

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

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

9.4.6.3 Details Concerning Timing and Dose Administration

9.4.6.3.1 Preparation and Administration

9.4.6.3.1.1 Preparation

Vials of pegloticase will be visually inspected for particulate matter and discoloration before administration, whenever solution and container permit. Vials will not be used if either is present. Using appropriate aseptic technique, 1 mL of pegloticase will be withdrawn from the vial into a sterile syringe. Any unused portion of product remaining in the vial will be discarded. Syringe contents will be injected into a single 250 mL bag of 0.45% or 0.9% Sodium Chloride Injection, USP for IV infusion and will not be mixed or diluted with other drugs. The infusion bag containing the dilute pegloticase solution will be inverted a number of times to ensure thorough mixing but will not be

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

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

9.4.6.3.1.2 Dose and Administration Pegloticase

All subjects will receive pegloticase at the same dose of 8 mg administered IV every 2 weeks for a total of 12 infusions from Day 1 through the Week 22 Visit. Subjects will not be fasting on the day of infusion and will be encouraged to have a snack or normal meal before or after the infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion (see Section 9.5.1.1).

Standardized IR prophylaxis consisting of pre-treatment with antihistamines, acetaminophen, and corticosteroids will accompany each infusion (see Section 9.4.1.2). The drug name, dose, and timing of these prophylactic medications will be recorded.

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

In a patent IV site, the pegloticase preparation will be infused over a period of no less than 120 minutes while the subject is under close observation for any signs of distress. No in-line

filter is required; however, 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 times of infusion start and stop (inclusive of the IV flush) will be recorded.

9.4.6.3.2 Dose Modifications, Interruptions, and Delays

9.4.6.3.2.1 Pegloticase Modifications

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

Infusions subsequent to an IR in an individual subject may be given in a larger volume of diluent, not to exceed 500 mL. In this case, the infusion duration will also be extended to a minimum of 3 hours. The total volume and duration of infusion will be captured in the medical record and eCRF.

9.4.6.3.2.2 Gout Flare Treatment

An increase in gout flares is frequently observed upon initiation of ULT, 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 9.5.4.10. All subjects who experience a gout flare during the study will be prescribed anti-inflammatory treatment (e.g., corticosteroids, colchicine, and intra-articular steroid injections), as is clinically indicated or deemed necessary on an individual basis at the discretion of the investigator (Becker , 2019). Pain medications for gout flare should be administered according to standard of care as is clinically indicated or deemed necessary on an individual basis at the discretion of the investigator. All medications should be documented on the concomitant medication eCRF.

Colchicine can be prescribed. The precise dose and regimen of colchicine should be individualized for each subject based on renal function and gastrointestinal intolerance by the Investigator and documented on the concomitant medication eCRF.

9.4.6.3.2.3 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 the possibility of an 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;
- 12-lead ECG will be performed;
- A serum sample will be collected in a serum-separating tube at that time or at the subsequent visit. The sample will be centrifuged, frozen at -20°C or colder, and stored for the batch shipment to a Horizon designated laboratory for evaluation of pegloticase antibodies at a future date.

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

The Investigator may administer any medically indicated pharmacologic agent or procedure intended to relieve symptoms (CAUTION: no other drugs can be mixed in the pegloticase infusion bag). Signs

and symptoms of the AE and drugs given for treatment are to be recorded in the medical record and in the eCRF.

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

9.4.7 Method of Assigning Subjects to Pegloticase

Medidata Randomization and Trial Supply Management (RTSM) will be used to assign subjects specific pegloticase kit numbers.

Specific procedures for accessing and assigning study drug through Medidata are contained in the study procedures manual.

9.4.8 Blinding

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

9.4.9 Prior and Concomitant Therapy

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

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

Information about prior and concomitant medications, including those used for any duration to treat an AE, will be collected on source documents and the appropriate eCRFs at each visit. The generic name of the medication, indication, dose, unit, frequency, route of administration, and start and stop dates will be recorded.

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

9.4.10 Restricted Medications

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

- Oral ULTs including allopurinol, febuxostat, probenecid, lesinurad, or other ULT for gout; Re-introduction of oral ULTs should not start until after the End of Pegloticase Visit (or End of Study) laboratory tests are collected.

- Any PEG-conjugated drug; nor
- Any other investigational agent

9.4.11 Treatment Compliance

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

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

9.4.12 Contraception Requirements

Women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to screening, or not surgically sterile [absence of ovaries and/or uterus]) must agree to use a medically approved form of birth control during their participation in the study.

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 by sUA levels, tophus size and resolution, urate deposition volume (using DECT), blood pressure, renal function, gout flare and physician global assessment of gout. Assessment of BP, eGFR and UACR are described in Section 9.5.1.4. These variables are also part of safety assessments.

9.5.1.1 Serum Uric Acid

Serum samples for measurement of sUA levels will be collected at the Screening Visit, prior to and after the end of each pegloticase infusion during the pegloticase treatment period. .

Additional serum samples for sUA levels will be collected at non-infusion Visits at Weeks 21 and 23, the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit and the 3-month Follow-up Visit. Subjects with an sUA level >6 mg/dL at

2 consecutive study visits beginning with the Week 2 Visit will discontinue pegloticase and will be encouraged to continue study participation through Week 24.

Two separate samples/tubes of blood should be collected within 48 hours prior to the pegloticase infusion if the previous visit's pre-infusion sUA value is > 6 mg/dL (except on Day 1 when only 1 pre-infusion sample is required for the central laboratory). One sample/tube will be assessed by the site's local laboratory to be used for on-study subject management; pre-infusion sUA results must be reported by the local or central laboratory prior to each pegloticase infusion if the previous visit's pre-infusion sUA value is > 6mg/dL. If a local laboratory sample is drawn (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase

infusion on the day of the visit. The second sample/tube will be sent to the central laboratory for analysis and recording in the database. See the Laboratory Manual for instructions for alternate scenarios.

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

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

Hand held uric acid measurement devices maybe provided to measure subject uric acid levels in real time. If hand held devices are provided, blood uric acid levels obtained from the device prior to pegloticase infusion will NOT be used to manage pegloticase treatment.

9.5.1.2 Hand Held Uric Acid Measurement Device

Select sites and patients may be provided with FDA approved devices to measure subject uric acid levels using a hand-held device. Results will be collected pre-infusion and post-infusion and used for exploratory uses only. No in-study treatment decisions will be made based upon the data generated with the hand held device.

9.5.1.3 Physician Global Assessment

The physician global assessment will be collected at Screening and prior to pegloticase infusion at the Day 1 and Week 6, 14, 20, End-of-Pegloticase-Infusions Visit (if applicable), and the Week 24/End-of-Study/Early Termination Visit (Section 2.1). The physician will respond to the statement, "Considering the subject's overall health related to gout, rate their gout overall" using a numeric rating scale ranging from 0 (excellent) to 10 (very poor) (see Appendix 17.3).

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

9.5.1.4 Dual-energy Computed Tomography (DECT)

For sites with DECT capability, DECT will be obtained between the Screening Visit (after all eligibility criteria have been confirmed) and the Day 1 Visit, the Week 14 Visit, the

End-of-Pegloticase-Infusions Visit (if applicable), and at the Week 24/End-of-Study/Early Termination Visit. The DECT may be completed within ± 7 days of the Week 14 and Week 24 Visits.

Subjects who end pegloticase infusions prior to Week 24 should follow the scheduled timepoints but avoid a repeat DECT scan within 6 weeks of a prior scan (detailed guidance is provided within the imaging manual).

Images will be obtained for the knees, hands/wrists and feet/ankles. The imaging will be performed by a study-specific, qualified radiologist.

9.5.1.5 Digital Photography

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

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

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

9.5.1.5.1 Assessment of Individual Tophi Response

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

- Complete Response (CR) – A 100% decrease in the area of the tophus;
- Marked Response (MR) – At least a 75% decrease in the area of the tophus;
- Partial Response (PR) - At least a 50% decrease in the area of the tophus;
- Stable Disease (SD) – Neither a 50% decrease nor a 25% increase in the area of the tophus can be demonstrated;
- Progressive Disease (PD) – A 25% or more increase in the area of the tophus; or
- Unable to Evaluate (UE) –The tophus cannot be accurately measured for any reason at any given post-baseline time point (e.g., image missing or of poor quality, obvious infection of the tophus).

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

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

The overall response for a subject will be based upon the best response among all tophi (including measurable and unmeasurable) for that subject (e.g., if any one tophus shows complete response, the

overall response is Complete Response). If any single tophus shows progression, or if a new tophus appears during the study, the overall response for that subject will be Progressive Disease, regardless of the response of any other tophi.

9.5.2 Quality of Life Assessment

The HAQ (Appendix 17.2) including the HAQ-DI, pain and health scales, will be administered at Screening and prior to the pegloticase infusion at the Day 1 Visit, the Week 6 and 14 Visit, the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit, and the 3-month Post-Treatment Follow-up Visit (Section 2.1).

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

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

[redacted]

9.5.3 Pharmacokinetic and Anti-drug Antibody Measurements

Serum samples for PK analysis of pegloticase will be collected after the end of infusion on Day 1 (prior to discharge); prior to the pegloticase infusion and after the end of the infusion (prior to discharge) at Weeks 2, 6, 14, and 22. Additional PK samples will be collected at the Week 21 Visit, the End-of-Pegloticase-Infusions Visit (if applicable), and the Week 24/End-of-Study/Early Termination Visit.

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

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

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

9.5.4 Safety Variables

Safety will be assessed via AE and concomitant medication use monitoring, physical examinations, vital signs, clinical safety laboratory evaluations (hematology, chemistry, urine albumin:creatinine ratio, eGFR), pregnancy testing (if applicable), electrocardiograms (ECGs), and AEs of special interest (i.e., IRs, anaphylaxis, gout flares, and CV events) and incidence of biopsy confirmed renal rejection.

9.5.4.1 Adverse Events

9.5.4.1.1 Definitions

9.5.4.1.1.1 Adverse Event Definition

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

Examples of an AE include:

- Conditions newly detected or diagnosed after the signing of the ICF, including conditions that may have been present but undetected prior to the start of the study;
- Conditions known to have been present prior to the start of the study that worsen after the signing of the ICF;
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction; 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 study, should be recorded as medical history;
- Medical or surgical procedures (e.g., endoscopy, appendectomy; however, a condition that leads to a procedure is an AE if it qualifies according to the definitions above);
- Situations where an untoward medical occurrence did not occur (e.g., social, diagnostic, elective, or convenience admission to a hospital);
- Fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not represent a clinically significant change from baseline; 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:

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

or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. If in doubt as to whether or not an event qualifies as an 'important medical event,' consult the Sponsor's Medical Monitor.

9.5.4.1.1.3 Non-Serious Adverse Event Definition

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

9.5.4.1.1.4 Unexpected Adverse Event Definition

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

9.5.4.1.1.5 Adverse Events of Special Interest

AEs of special interest include IRs, anaphylaxis, gout flares, and CV events. An external adjudication committee will adjudicate the AESIs of IR, anaphylaxis and CV events.

Infusion Reaction

An IR will be defined as any infusion-related AE or cluster of temporally-related AEs, not attributable to another cause, which occur during the pegloticase infusion and for up to 2 hours post-infusion. Other AEs that occur outside of the 2-hour window following the infusion may also be categorized as an IR at the PI'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 2 hours following the infusion (e.g., anemia), gout flares, most infectious diseases, or the recurrence or worsening of a known chronic medical problem identified in the subject's medical history.

Anaphylaxis

Any incidence of anaphylaxis should be reported as an SAE. Anaphylaxis will be defined using the NIAID/FAAN 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); and
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue, uvula);
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia);
   c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence); and
   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 ULTs to lead to acute attacks of gout. Gout flares will be confirmed through questioning the subject or direct observation by the Investigator and will be recorded as AEs.

Cardiovascular Events

Cardiovascular AEs will be collected as part of the AE recording. External adjudication will be conducted for selected CV events. Refer to the Adjudication Committee Charter for the detailed definition.

9.5.4.1.1.6 Biopsy Confirmed Acute Rejection

The incidence of renal rejection confirmed by biopsy will be collected as part of the AE recording.

9.5.4.1.2 Documentation of Adverse Events

AE monitoring will begin from the signature of the ICF until the 3-month Post-Treatment Follow-up Visit.

SAE monitoring will begin from the signature of the ICF until the 3-month Post-Treatment Follow-up Visit.

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

9.5.4.1.3 Intensity of Adverse Events

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

values) based on this general guideline. See the Study Reference Manual for details. AEs that do not have a corresponding RCTC term will be assessed for severity based on following criteria:

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

9.5.4.1.4 Relationship to Study Drug

The relationship of each AE to 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; and
  - There is a distinguishable dose effect.

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

9.5.4.1.5 Reporting and Documenting SAEs and Product Complaints

9.5.4.1.5.1 Serious Adverse Events

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

Fax [redacted]

Email [redacted]

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

1. Report the SAE to the Sponsor by entering the information into the eCRF within 24 hours after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form by email to [redacted] or fax within 24 hours after becoming aware that a subject has experienced an SAE;
2. Perform appropriate diagnostic tests and therapeutic measures, and submit all follow-up substantiating data, such as diagnostic test reports, hospital discharge summaries, and autopsy report to the Sponsor's representative;
3. Respond in a timely manner to any queries from Sponsor regarding the SAE;
4. Conduct appropriate consultation and follow-up evaluation until the SAE is resolved, stabilized, or otherwise explained by the Investigator;
5. Review each SAE report and evaluate the relationship of the SAE to pegloticase; and
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 email, as necessary, until the event resolves or attains a stable outcome. Horizon or designee is responsible for the preparation of

MedWatch 3500 A/Council for International Organizations of Medical Sciences I forms and analysis of similar events for individual occurrences (to be submitted as Investigational New Drug [IND] safety letters to the FDA and Investigators according to 21 CFR 312.32 by Horizon).

9.5.4.1.5.2 Product Complaints

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

9.5.4.1.6 Follow-up of Adverse Events

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

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

9.5.4.1.7 Medication Error and Overdose

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

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

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

9.5.4.1.8 Review of Adverse Events and Emerging New Safety Information

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

9.5.4.1.9 Reporting of IND Safety Reports

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

9.5.4.1.10 Development Safety Update Reports

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

9.5.4.2 Pregnancy Reporting

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

Information must be obtained and reported if a female subject suspects that she has become pregnant during the study up to 30 days after the last dose of study treatment. The Investigator will instruct the female subject to stop taking all study drugs. A serum pregnancy test should be performed if any female subject suspects that she has become pregnant during the time frame as defined above. If pregnancy is confirmed, female subject will be withdrawn from the study. Pregnancy will be followed up until the outcome of pregnancy.

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

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

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

9.5.4.3 Medical History

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

9.5.4.4 Vital Signs, Height, and Weight

Routine vital signs, including blood pressure, respiratory rate, temperature, and heart rate will be measured at Screening, Day 1 and Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, the

End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit and the 3-month Post-Treatment Follow-up Visit (before any scheduled blood draws).

Heart rate and BP measurements should be taken after the subject has been in a sitting position and in a rested and calm state with proper positioning including back support 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 the same arm is to be used consistently at each study visit. The Korotkoff phase V will be used to determine DBP. The cuff deflation rate should be 2 mm Hg per second.

During the pegloticase treatment period study 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.

Intensive BP measurements will be taken prior to the infusion on Day 1 and at the Week 6, 12, and 18 Visits, the End-of-Pegloticase-Infusions Visit (if applicable), and the Week 24/End-of-Study/Early Termination Visit. At these intensive BP collections, three BP measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 SBP measurements differ by more than 8 mm Hg or if DBP measurements differ by more than 5 mm Hg, additional sets of 3 sitting BP measurements will be obtained until the measurements differ by less than 8 mm Hg (SBP) and 5 mm Hg (DBP). All values will be recorded in the eCRF.

Every effort should be made to standardize the conditions of clinic BP measurements at each visit whenever possible. The same arm and same cuff size should be used. When possible, the same staff member should take all BP measurements for a given subject.

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

Vital sign monitoring during IR is described in Section 9.4.6.3.2.3.

9.5.4.5 Physical Examinations

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

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

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

9.5.4.6 Electrocardiogram

A 12-lead ECG will be performed at Screening and at the discretion of the Investigator thereafter. When a subject experiences an AE suspected to be an IR, a 12-lead ECG will also be performed.

9.5.4.7 Clinical Laboratory Safety Tests

Blood (for hematology and clinical chemistry) will be collected at Screening, prior to the pegloticase infusion on Day 1 and at the Week 2, 6, 14, and 22 Visits, the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit and 3-month Post-Treatment Follow-up Visit.

Urine (for albumin:creatinine ratio) samples will be collected at Screening, prior to the pegloticase infusion on Day 1 and at the Week 6, 14, and 22 Visits, the End-of-Pegloticase-Infusions Visit (if applicable) and Week 24/End-of-Study/Early Termination Visit.

Urine (for human chorionic gonadotropin) samples will be collected at selected visits. Safety laboratory assessments will include:

- Hematology: complete blood count with differential (hemoglobin concentration, hematocrit, erythrocyte count, platelet count, leukocyte count, and differential leukocyte count);
- Chemistry: albumin, transaminases (aspartate aminotransferase, alanine

aminotransferase), alkaline phosphatase, total bilirubin, creatinine (including calculation for eGFR calculated by the Modification of Diet in Renal Disease [MDRD] study equation : 175 x $(S_{cr[mg/dL]})^{-1.154}$ x $(age)^{-0.203}$x (0.742 if female) x (1.212 ifAfrican American) or 175 x $(S_{cr[\mu mol/L]}/88.4)^{-1.154}$ x $(age)^{-0.203}$x (0.742 if female) x (1.212 if African American), glucose, sodium, potassium, calcium, chloride, total protein, blood urea nitrogen, and human chorionic gonadotropin (at the Screening Visit and the Week 24/End-of-Study/Early Termination Visit for all female subjects of childbearing potential); 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.

9.5.4.8 Blood and Urine Sample for Potential Analysis of Allantoin

Blood and urine samples will be collected prior to pegloticase infusion on Day 1 and at the pre-infusion Week 2, 4, 6, 8, 10, 14, 18, and 22 Visits, the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit, and the 3-month Post-Treatment Follow-up Visit. In addition, blood and urine samples will be collected after the end of pegloticase infusions prior to discharge from the site on Day 1, Week 2, 6, 14 and 22 Visits. Both allantoin and creatinine will be analyzed in urine samples collected at these visits to calculate allantoin:creatinine ratio.

9.5.4.9 Blood Samples for Potential Analysis of Biomarkers

Optional blood samples for peripheral blood mononuclear cells (PBMC) and serum will be collected from each consenting subject at Screening, the Week 8 and 14 Visits, the End-of-Pegloticase-Infusions Visit (if applicable), and the Week 24/End-of-Study/Early Termination Visit. Subjects who fail Screening will also be requested to provide at least 1 additional blood sample 24 weeks +/- 4 weeks after the initial sample collection. An unscheduled visit will be arranged at that time to also collect adverse events, concomitant medications, blood samples for hematology and clinical chemistry and vital signs.

Exploratory inflammatory biomarkers including cytokine levels, cell surface markers, messenger ribonucleic acid (mRNA) expression, and markers-related transplant outcome, gout or gout co-morbidities in response to pegloticase or other potential treatment for gout may be analyzed.

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

9.5.4.10 Assessment of Gout Flare

There is no validated instrument to assess gout flares. Investigator's reported gout flare will be recorded as adverse events with the required AE reporting information in the eCRF per

Section 9.5.4.1.1.5. In addition to investigator reporting, subjects will be asked to fill out a subject-reported gout flare questionnaire 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) (Appendix 17.4) at each visit for exploration of subject-reporting vs. investigator reporting of flares.

9.5.5 Adjudication Committee

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

9.5.6 Appropriateness of Measurements

The study population is well-defined and is consistent with the expected target population for whom pegloticase is indicated (adult subjects with uncontrolled gout refractory to standard ULT and with kidney transplant).

9.5.7 Study Procedures

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

9.5.7.1 Screening Period

During the Screening Period, study candidates will be evaluated for study entry according to the stated inclusion and exclusion criteria (Section 9.3). The procedures in Section 9.5.7.1.1 will be performed during Screening to establish each candidate's eligibility for enrollment into the study.

9.5.7.1.1 Screening Visit (Within 35 Days of the Day 1 Visit)

- Obtain signed, written informed consent. Refusal to provide this consent excludes an individual from eligibility for study participation. Record date informed consent was given and who conducted the process on the appropriate source documentation:
- Determine study eligibility through review of the inclusion/exclusion criteria (see Section 9.3);
- Obtain demographic information;
- Investigator review of clinical status and subject treatment goals.;
- Collect complete gout history (on gout-specific CRF), other relevant medical/surgical history, and medication history, including gout medications starting at the time of diagnosis and up to screening (on gout medications-specific CRF), substance use history, and all other medications currently being taken at Screening (see Section 9.4.10 for restrictions regarding medications);

- Perform a complete physical examination, including assessment of HEENT, heart, lungs, abdomen, skin, extremities, neurological status and musculoskeletal including an assessment for the presence of tophi;
- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) (see Section 9.5.4.4);
- Record height and weight;
- [redacted]
- Perform 12-lead ECG;
- Obtain blood samples for hematology and clinical chemistry analysis;
- Obtain a serum sample from all females of childbearing potential for performance of a pregnancy test;
- Obtain blood samples to evaluate sUA (only 1 sample for central laboratory), G6PD and HBV serology;
- If hand held device is provided, perform fingerstick for uric acid measurement;
- Obtain spot urine sample for albumin:creatinine ratio;
- Obtain whole blood and serum samples for potential analyses of biomarkers from consenting subjects;
- Administer HAQ [redacted]
- Administer subject self-reported gout flare assessment questionnaire;
- Inquire about AEs and concomitant medication use; and
- [redacted]

9.5.7.2 Pegloticase Treatment Period

9.5.7.2.1 Day 1

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

- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdomin);
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4). [redacted]

[redacted]

- Determine study eligibility through review of the inclusion/exclusion criteria (see Section 9.3);
- Record weight;
- [redacted]
- [redacted]
- Administer HAQ [redacted]
- Administer subject self-reported gout flare assessment questionnaire;
- Obtain blood samples for hematology and clinical chemistry analysis;
- Obtain a urine sample for albumin:creatinine ratio;
- Obtain blood and urine samples for allantoin prior to pegloticase infusion and after the end of the infusion prior to discharge from the site;
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test;
- Obtain 1 blood sample for measurement of sUA prior to the pegloticase infusion and after the end of the pegloticase infusion;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Administer the first dose of pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain blood samples for pegloticase PK analysis any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.2 **Week 2**

- Obtain 1 blood sample to be sent to the central lab for measurement of sUA prior to the pegloticase infusion;
- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase

infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4);

- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Administer subject self-reported gout flare assessment questionnaire;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Obtain blood samples for hematology and clinical chemistry analysis;
- Obtain spot urine sample for albumin:creatinine ratio;
- Obtain blood samples for pegloticase PK analysis prior to the pegloticase infusion and any time after the end of the infusion, prior to discharge from the site;
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion;
- Obtain blood and urine samples for allantoin prior to pegloticase infusion and after the end of the infusion prior to discharge from the site;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.3 **Week 4**

- For subjects with a pre-infusion sUA value of > 6 mg/dL at the previous visit, obtain 1 blood sample for measurement of sUA by the local lab within 48 hours prior to this Visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local laboratory prior to pegloticase infusion. An additional pre-infusion blood sample for measurement of sUA will be drawn on the day of the visit and sent to the central lab. For subjects with pre-infusion sUA <= 6 at the previous visit, only the pre-infusion sample on day of visit for central lab is needed. (see Section 9.5.1.1);
    - Stopping rule: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- Perform a targeted physical examination (at a minimum this should include heart, lungs and

abdomen);

- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4);
- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Administer subject self-reported gout flare assessment questionnaire;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test;
- Obtain whole blood and serum samples for potential analyses of biomarkers from consenting subjects;
- Obtain blood and urine samples for allantoin;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.4 **Week 6**

- For subjects with a pre-infusion sUA value of > 6 mg/dL at the previous visit, obtain 1 blood sample for measurement of sUA by the local lab within 48 hours prior to this Visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local laboratory prior to pegloticase infusion. An additional pre-infusion blood sample for measurement of sUA will be drawn on the day of the visit and sent to the central lab. For subjects with pre-infusion sUA <= 6 at the previous visit, only the pre-infusion sample on day of visit for central lab is needed.(see Section 9.5.1.1);
  - Stopping rule: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase

infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4). [redacted]

- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Administer HAQ [redacted]
- Administer subject self-reported gout flare assessment questionnaire;
- Obtain blood samples for hematology and clinical chemistry analysis;
- Obtain spot urine sample for albumin:creatinine ratio;
- Obtain blood and urine samples for allantoin prior to pegloticase infusion and after the end of infusion prior to discharge from the site;
- Obtain blood samples for pegloticase PK analysis prior to the pegloticase infusion and any time after the end of the infusion, prior to discharge from the site;
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.5 **Week 8**

- For subjects with a pre-infusion sUA value of > 6 mg/dL at the previous visit, obtain 1 blood sample for measurement of sUA by the local lab within 48 hours prior to this Visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local laboratory prior to pegloticase infusion. An additional pre-infusion blood sample for measurement of sUA will be drawn on the day of the visit and sent to the central lab. For subjects with pre-infusion sUA <= 6 at the previous visit, only the pre-infusion sample on day of visit for central lab is needed. (see Section 9.5.1.1);
  - Stopping rule: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study;

- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdomen);
- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4);
- Record weight;
- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Administer subject self-reported gout flare assessment questionnaire;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test;
- Obtain blood and urine samples for allantoin;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.6 **Week 10**

- For subjects with a pre-infusion sUA value of > 6 mg/dL at the previous visit, obtain 1 blood sample for measurement of sUA by the local lab within 48 hours prior to this Visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local laboratory prior to pegloticase infusion. An additional pre-infusion blood sample for measurement of sUA will be drawn on the day of the visit and sent to the central lab. For subjects with pre-infusion sUA <= 6 at the previous visit, only the pre-infusion sample on day of visit for central lab is needed. (see Section 9.5.1.1);
  - Stopping rule: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;

- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4);
- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance.
- Administer subject self-reported gout flare assessment questionnaire;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Obtain blood and urine samples for allantoin;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use;

9.5.7.2.7 **Week 12**

- For subjects with a pre-infusion sUA value of > 6 mg/dL at the previous visit, obtain 1 blood sample for measurement of sUA by the local lab within 48 hours prior to this Visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local laboratory prior to pegloticase infusion. An additional pre-infusion blood sample for measurement of sUA will be drawn on the day of the visit and sent to the central lab. For subjects with pre-infusion sUA <= 6 at the previous visit, only the pre-infusion sample on day of visit for central lab is needed. (see Section 9.5.1.1);
  - Stopping rule: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdomen);
- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4). [redacted]

[redacted]

- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Administer subject self-reported gout flare assessment questionnaire;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.8 **Week 14**

- For subjects with a pre-infusion sUA value of > 6 mg/dL at the previous visit, obtain 1 blood sample for measurement of sUA by the local lab within 48 hours prior to this Visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local laboratory prior to pegloticase infusion. An additional pre-infusion blood sample for measurement of sUA will be drawn on the day of the visit and sent to the central lab. For subjects with pre-infusion sUA <= 6 at the previous visit, only the pre-infusion sample on day of visit for central lab is needed. (see Section 9.5.1.1);
  - Stopping rule: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4);
- Administer HAQ [redacted]
- Administer subject self-reported gout flare assessment questionnaire;

- [redacted]
- [redacted]
- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Obtain blood samples for hematology and clinical chemistry analysis;
- Obtain a urine sample for albumin:creatinine ratio;
- Obtain blood and urine samples for allantoin prior to pegloticase infusion and after the end of the infusion prior to discharge from the site;
- Obtain blood samples for pegloticase PK analysis prior to the pegloticase infusion and any time after the end of the infusion, prior to discharge from the site;
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion;
- Obtain whole blood and serum samples for potential analyses of biomarkers from consenting subjects;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.9 **Week 16**

- For subjects with a pre-infusion sUA value of > 6 mg/dL at the previous visit, obtain 1 blood sample for measurement of sUA by the local lab within 48 hours prior to this Visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local laboratory prior to pegloticase infusion. An additional pre-infusion blood sample for measurement of sUA will be drawn on the day of the visit and sent to the central lab. For subjects with pre-infusion sUA <= 6 at the previous visit, only the pre-infusion sample on day of visit for central lab is needed. (see Section 9.5.1.1);
  - Stopping rule: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study.
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;

- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdomen);
- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4);
- Record weight;
- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Administer subject self-reported gout flare assessment questionnaire;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.10 **Week 18**

- For subjects with a pre-infusion sUA value of > 6 mg/dL at the previous visit, obtain 1 blood sample for measurement of sUA by the local lab within 48 hours prior to this Visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local laboratory prior to pegloticase infusion. An additional pre-infusion blood sample for measurement of sUA will be drawn on the day of the visit and sent to the central lab. For subjects with pre-infusion sUA <= 6 at the previous visit, only the pre-infusion sample on day of visit for central lab is needed. (see Section 9.5.1.1);
  - Stopping rule: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- Obtain blood and urine samples for allantoin;
- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase

infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4). [redacted]

- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Administer subject self-reported gout flare assessment questionnaire;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.11 **Week 20**

- For subjects with a pre-infusion sUA value of > 6 mg/dL at the previous visit, obtain 1 blood sample for measurement of sUA by the local lab within 48 hours prior to this Visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local laboratory prior to pegloticase infusion. An additional pre-infusion blood sample for measurement of sUA will be drawn on the day of the visit and sent to the central lab. For subjects with pre-infusion sUA <= 6 at the previous visit, only the pre-infusion sample on day of visit for central lab is needed. (see Section 9.5.1.1);
  - Stopping rule: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdomen);
- [redacted]
- Administer HAQ [redacted]
- Administer subject self-reported gout flare assessment questionnaire;

- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4);
- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.12 **Week 21**

- Obtain a blood sample (1 sample) for measurement of sUA;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- Obtain blood samples for pegloticase PK analysis;
- Inquire about AEs and concomitant medication use;
- [redacted]
- Administer subject self-reported gout flare assessment questionnaire; and
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;

9.5.7.2.13 **Week 22**

- For subjects with a pre-infusion sUA value of > 6 mg/dL at the previous visit, obtain 1 blood sample for measurement of sUA by the local lab within 48 hours prior to this Visit's pegloticase infusion. Pre-infusion sUA results must be reported by the local laboratory prior to pegloticase infusion. An additional pre-infusion blood sample for measurement of sUA will be drawn on the day of the visit and sent to the central lab. For subjects with pre-infusion sUA <= 6 at the previous visit, only the pre-infusion sample on day of visit for central lab is needed. (see Section 9.5.1.1);
    - Stopping rule: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit (not including post-infusion samples) will subsequently discontinue treatment and remain in the study;

- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- [redacted]
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4);
- Ask Yes/No question regarding gout flare prophylaxis, and IR prophylaxis compliance;
- Administer subject self-reported gout flare assessment questionnaire;
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed;
- Obtain blood samples for hematology and clinical chemistry analysis;
- Obtain blood and urine samples for allantoin prior to pegloticase infusion and after the end of infusion prior to discharge from the site;
- Obtain a urine sample for albumin:creatinine ratio;
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.2);
- Obtain blood samples for pegloticase PK analysis prior to the pegloticase infusion and any time after the end of the infusion, prior to discharge from the site;
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion;
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop (inclusive of 10 mL flush) times of dosing;
- Obtain a blood sample (1 sample) for measurement of sUA any time after the end of the infusion, prior to discharge from the site; and
- Inquire about AEs and concomitant medication use.

9.5.7.2.14 **Week 23**

- Obtain a blood sample (1 sample) for measurement of sUA;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- Inquire about AEs and concomitant medication use;
- [redacted]
- Administer subject self-reported gout flare assessment questionnaire; and
- Fill gout prophylaxis, fexofenadine and acetaminophen prescriptions, as needed.

9.5.7.3 End-of-Pegloticase-Infusion Visit

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

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

- [redacted]
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdomen);
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4). [redacted]
- Record weight;
- Administer HAQ [redacted]
- Administer subject self-reported gout flare assessment questionnaire;
- Investigator review of clinical status and subject treatment goals;
- Ask Yes/No question regarding gout flare prophylaxis compliance;
- [redacted]
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test;
- Obtain blood samples for hematology and clinical chemistry analysis;
- Obtain a urine sample for albumin:creatinine ratio;
- Obtain blood and urine samples for allantoin;

- Obtain blood samples for pegloticase PK analysis;
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies;
- Obtain whole blood and serum samples for potential analyses of biomarkers from consenting subjects;
- Obtain a blood sample (1 sample) for measurement of sUA; and
- If hand held device is provided, perform fingerstick for uric acid measurement;
- Inquire about AEs and concomitant medication use.

9.5.7.4 Week 24/End-of-Study/Early Termination Visit

- [redacted]
- Investigator review of clinical status and subject treatment goals;
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdomen).
- Record vital signs (BP, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion and any time after the end of the infusion, but prior to discharge (see Section 9.5.4.4). [redacted]
- Record weight;
- Administer HAQ [redacted]
- Administer subject self-reported gout flare assessment questionnaire;
- [redacted]
- [redacted]
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test;
- Obtain blood samples for hematology and clinical chemistry analysis;
- Obtain blood and urine samples for allantoin;
- Obtain blood samples for pegloticase PK analysis;
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies;
- Obtain whole blood and serum samples for potential analyses of biomarkers from consenting subjects;

- Obtain a blood sample (1 sample) for measurement of sUA; and
- If hand held device is provided, perform fingerstick for uric acid measurement;
- Inquire about AEs and concomitant medication use.

9.5.7.5 Safety Follow-up Phone/Email Visits

Thirty (30) days after the last pegloticase infusion, subjects will be contacted by telephone or email to inquire about SAEs.

9.5.7.6 Post-Treatment Follow-up

The intent is to obtain at least 3 months of follow-up on each subject after cessation of pegloticase infusions. If the subject ends treatment early but remains in the study and the 3- month Post Treatment Follow-up Visit occurs prior to Week 24, the 3-month Post Treatment Follow-up Visit will be adjusted accordingly based on the timing of the last treatment.

The following procedures will be completed at the 3-month Post-Treatment Follow-up Visit:

- [redacted]
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to discharge (see Section 9.5.4.4);
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdomen);
- Record weight;
- Administer HAQ [redacted]
- Administer subject self-reported gout flare assessment questionnaire;
- [redacted]
- Obtain blood samples for hematology and clinical chemistry analysis;
- Obtain a blood sample (1 sample) for measurement of sUA;
- If hand held device is provided, perform fingerstick for uric acid measurement prior to the pegloticase infusion and after the end of the pegloticase infusion;
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies (3-month Post-Treatment Follow-up Visit only);
- Obtain blood and urine samples for allantoin; and
- Inquire about AEs and concomitant medication use.

9.6 Statistical Methods and Determination of Sample Size

9.6.1 Endpoints

9.6.1.1 Primary Endpoint:

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

9.6.1.2 Secondary Endpoints

The secondary efficacy endpoints are:

- The proportion of 5 mg/dL responders during Month 6 (Weeks 20, 21, 22, 23 and 24), defined as subjects achieving and maintaining sUA < 5 mg/dL for at least 80% of the time during Month 6;
- The change from baseline in mean HAQ pain score to Week 24; and
- The change from baseline in mean HAQ-DI score to Week 24.

9.6.1.3 [redacted]

[redacted]

[redacted]

9.6.1.4 Pharmacokinetic and Anti-drug Antibody Endpoints

The PK and anti-drug antibody endpoints are:

- Serum concentrations of pegloticase; and
- Profile of anti-PEG and anti-uricase IgG antibodies.

9.6.1.5 Safety and Tolerability Endpoints

Safety and tolerability objectives are:

- Overall AE/SAE profile;
  - Incidences of AESI: IRs, anaphylaxis, gout flares, cardiovascular events;
- Laboratory tests;
- Vital signs and physical examination; and
- Incidence of renal rejection (biopsy proven).

9.6.2 Populations for Analysis

The following analysis populations will be defined for this study:

- Modified intent-to-treat (mITT) population: all subjects who receive at least 1 dose of pegloticase; and
- Pharmacokinetic (PK) population: all subjects who receive at least 1 dose of pegloticase and have a post-pegloticase sample evaluable for PK analysis.

The mITT population will be used for analysis of efficacy and safety data.

9.6.3 Demographic Variables

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

9.6.4 Subject Disposition

The number of subjects in each population and the number and percentage of subjects who complete the study, who discontinue therapy before the Week 22 infusion, and who discontinue the study prematurely along with the reasons for discontinuation will be summarized.

9.6.5 Efficacy Endpoint Analysis

Efficacy analyses will be performed using the mITT population. No formal statistical testing will be performed, and there is no adjustment for multiplicity in this open-label study.

Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages. Unless otherwise specified, baseline is defined as the last non-missing observation prior to the first dose of pegloticase.

9.6.5.1 Primary and Secondary Endpoint Analysis

The primary efficacy endpoint is the proportion of responders during Month 6. A responder is defined as a subject for whom the proportion of time that the sUA-time curve is <6 mg/dL during the analysis interval is at least 80%. The proportion of time that the sUA level is below 6 mg/dL is defined as the ratio of the time during which the sUA level remains below 6 mg/dL (using linear interpolation, if necessary) to the entire time interval during Month 6. The proportion of responders will be summarized, along with a 95% exact (Clopper-Pearson) confidence interval (CI) for the proportion.

A subject will be declared a non-responder if the subject had 2 pre-infusion sUA levels>6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit and prior to or during Month 6. Additionally, a subject who withdraws from study treatment for any reason other than the stopping rule after the first dose of pegloticase and prior to or during Month 6 will be considered a non-responder if sUA values are not collected at planned timepoints. Special consideration may be given to subjects who discontinue the study or miss visits due to reasons related to the COVID-19 pandemic.

The mean change from baseline to each visit in HAQ pain score and HAQ-DI score will be summarized with descriptive statistics, including 95% CIs for the change from baseline.

9.6.5.2 Exploratory Endpoint Analysis

[redacted]

[redacted]

9.6.6 Pharmacokinetic and Anti-drug Antibody Analysis

Concentrations for pegloticase will be summarized using descriptive statistics for the PK population.

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

9.6.7 Safety Analysis

Treatment-emergent AEs are defined as events with an onset date on or after the start of the first pegloticase infusion through 30 days after the last dose of pegloticase. AEs that occur more than 30 days after the last dose of pegloticase through the 3-month follow-up visit will also be summarized.

The number and percentage of subjects experiencing AEs will be summarized by system organ class and preferred term. Summaries by maximum severity and relationship to study drug will also be provided. SAEs and AEs leading to discontinuation of study drug will be presented by system organ class and preferred term. The proportion of subjects with each AESI will also be summarized.

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

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

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

9.6.8 Interim Analyses

No formal interim analysis is planned for this study. Efficacy and safety data may be summarized after 10-15 subjects have been followed through Week 24. Additional summary of the data may be performed periodically throughout the study, and safety data will be summarized regularly for safety monitoring. Final analysis will occur when all subjects have completed the study.

9.6.9 Sample Size and Power Considerations

A sample size of 20 subjects is planned for this study. The primary efficacy endpoint, the proportion of subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6, will be demonstrated to be statistically greater than 43.5% (proportion of responders during Month 6 in the Phase 3 studies), if at least 14/20 (70%) responders are observed. In that case, the lower bound of a 95% confidence interval for the proportion of responders will be about 46%.

9.7 Changes in the Conduct of the Study

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

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

The Sponsor has a legal responsibility to report fully to regulatory authorities all results of administration of investigational drugs to humans. No investigational procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB and Sponsor.

10 SOURCE DOCUMENTATION AND INVESTIGATOR FILES

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

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

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

11 CASE REPORT FORMS

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

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

12 STUDY MONITORING

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

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

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

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

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

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

Every effort will be made to maintain the anonymity and confidentiality of subjects participating in this clinical study. However, because of the investigational nature of this treatment, the Investigator agrees to allow representatives of the Sponsor, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and to have direct access to inspect, for purposes of verification, the hospital or clinical records of all subjects enrolled in this study. A statement to this effect should be included in the ICF.

13 DATA MANAGEMENT

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

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

14 RETENTION OF RECORDS

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

15 PUBLICATION

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

16 REFERENCES

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17 APPENDICES

17.1 Administrative Appendix

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

Clinical Monitor	[redacted] [redacted] Horizon Therapeutics USA, Inc. 150 S. Saunders Road Lake Forest, IL 60045 Mobile telephone number: [redacted] Fax number: [redacted] Email: [redacted]
Sponsor Representative	[redacted] [redacted] Horizon Therapeutics USA, Inc. 150 S. Saunders Road Lake Forest, IL 60045 Mobile telephone number: [redacted] Fax number: [redacted] Email: [redacted]
Sponsor Contact for Serious Adverse Event Reporting	[redacted] Fax number: [redacted] Email: [redacted]
24-hour Phone Contact for Safety Coverage	Med Communications Phone number: [redacted]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

No Pain — **Severe Pain**

0 — **100**

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

Very Well — **Very Poor**

0 — **100**

17.3 Physician Global Assessment

PHYSICIAN GLOBAL ASSESSMENT

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

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

17.4 Subject Self-Reported Gout Flare Assessment

Gout flare since last visit

Have you had a gout attack (flare) since your last visit or in the past two weeks (for the Screening Visit)? ☐ Yes ☐ No

If yes, how many? _____

(please complete one set of questions for each flare)

Flare 1

Were any of your joints swollen at that time? ☐ Yes ☐ No

Were any of your joints warm to the touch at that time? ☐ Yes ☐ No

Considering the pain associated with your prior symptoms when you were resting (for example in bed or sitting quietly), please circle the number indicating the level of pain when it was at its worst, how would rate that pain?

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

Flare 2

Were any of your joints swollen at that time? ☐ Yes ☐ No

Were any of your joints warm to the touch at that time? ☐ Yes ☐ No

Considering the pain associated with your prior symptoms when you were resting (for example in bed or sitting quietly), please circle the number indicating the level of pain when it was at its worst, how would rate that pain?

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

Flare 3

Were any of your joints swollen at that time? ☐ Yes ☐ No

Were any of your joints warm to the touch at that time? ☐ Yes ☐ No

Considering the pain associated with your prior symptoms when you were resting (for example in bed or sitting quietly), please circle the number indicating the level of pain when it was at its worst, how would rate that pain?

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

Gout flare today

Are you having a gout attack (flare) today? ☐ Yes ☐ No

Are any of your joints swollen? ☐ Yes ☐ No

Are any of your joints warm to the touch? ☐ Yes ☐ No

Considering pain from your gout over the past 1 week when you were resting (for example in bed or sitting quietly), please circle the number indicating the level of pain when it was at its worst, how would rate that pain?

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