CLINICAL STUDY PROTOCOL FOR PEGLOTICASE

IND: 010122

Protocol Number: HZNP-KRY-403

Version 5.0, Amendment 4

A Phase 4, Multicenter, Open-Label, Infusion Duration Study To Assess Safety, Tolerability and Efficacy of Pegloticase Administered With a Shorter Infusion Duration in Subjects with Uncontrolled Gout Receiving Methotrexate

Date: 09 NOV 2022

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

PROTOCOL

1 TITLE PAGE

Study Title:	A Phase 4, Multicenter, Open-Label, Infusion Duration Study To Assess Safety, Tolerability and Efficacy of Pegloticase Administered With a Shorter Infusion Duration in Subjects with Uncontrolled Gout Receiving Methotrexate
Protocol Number:	HZNP-KRY-403
Version:	5.0, Amendment 4
Investigational Products:	Pegloticase (recombinant modified mammalian urate oxidase [uricase])
Indication:	Chronic gout refractory to conventional therapy in adult patients
Sponsor:	Horizon Therapeutics Ireland DAC 70 St. Stephen's Green Dublin 2 Ireland D02 E2X4
Development Phase:	4
Sponsor's Responsible Medical Officer:	[redacted] M.D. Medical Director, Rare Disease Horizon Therapeutics U.S.A., Inc. Two Tower Place, 12th Floor South San Francisco, CA 94080
Sponsor Signatory:	[redacted] M.D. Medical Director, Rare Disease Horizon Therapeutics U.S.A., Inc. Two Tower Place, 12th Floor South San Francisco, CA 94080
Approval Date:	09NOV2022

CONTACT IN THE EVENT OF AN EMERGENCY

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

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

SPONSOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-403

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Version Date: 09NOV2022

Approved by:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
[redacted]-2022 | 12:10 CST
3AD156E57E094F3E8DBDCC6E35209500

11-Nov-2022 | 12:11 CST

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Director, Biostatistics
Horizon Therapeutics U.S.A., Inc.

Date

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Signer Name: [redacted]
Signing Reason: I approve this document
[redacted]-Nov-2022 | 12:56 CST
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11-Nov-2022 | 12:56 CST

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Horizon Therapeutics U.S.A., Inc.

Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-403

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Protocol Title: A Phase 4, Multicenter, Open-Label, Infusion Duration Study To Assess Safety, Tolerability and Efficacy of Pegloticase Administered With a Shorter Infusion Duration in Subjects with Uncontrolled Gout Receiving Methotrexate

Version Date: 09NOV2022

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

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

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

Signature:

Name Study Center Address City State Country	Date

SUMMARY TABLE OF CHANGES

Protocol Version 1.0, Original (20 April 2020) to
Protocol Version 2.0, Amendment 1 (14May2020)
Protocol Version 3.0, Amendment 2 (07JUL2020)
Protocol Version 4.0, Amendment 3 (14FEB2022)
Protocol Version 5.0 Amendment 4 (09NOV2022)

The table below highlights the primary changes to Version 5 of the Protocol. Administrative and typographical updates have also been made. Track changes version of the protocol can be provided on request.

Text **Version 4.0, Amendment 3** **14FEB2022**	**Amended Text** **Version 5.0, Amendment 4** **09NOV2022**	**Reason for Change**
Number and Country of Study Sites: Approximately 25 study centers in the United States.	**Number and Country of Study Sites:** Approximately 40 study centers in the United States.	*Increased estimated number of sites to support enrollment of the increased sample size.*
Overall Study Objective (Synopsis and Section 9): The overall objective of this study is to assess the tolerability and efficacy of pegloticase administered with a shorter infusion duration in subjects with uncontrolled gout receiving methotrexate and select the shortest infusion duration able to be well tolerated.	**Overall Study Objective (Synopsis and Section 9):** The overall objective of this study is to assess the tolerability and efficacy of pegloticase administered with a shorter infusion duration in subjects with uncontrolled gout receiving methotrexate.	*Updated objective to simplify.*
Study Design (synopsis and Section 9.1): Approximately 80 subjects will be enrolled.	**Study Design (synopsis and Section 9.1):** Approximately 10 subjects in each cohort are planned to be enrolled initially. If deemed safe, an additional 100 subjects to be enrolled in the selected cohort in order to have approximately 110 subjects exposed.	*Updated to reflect targeted sample size.*
Study Design (synopsis and Section 9.1): Cohorts of approximately 10 subjects will be enrolled sequentially at progressively shorter infusion durations, beginning with the 60-minute infusion duration, progressing down to the 45-minute infusion duration and then to the 30-minute infusion duration. If deemed safe, enrollment will continue until approximately 60 subjects are enrolled in the last infusion duration cohort (e.g. 60 subjects in the 30-minute infusion cohort, unless 30-minute infusion was not tolerated and then approximately 60 subjects may be enrolled in the 45-minute infusion cohort).	**Study Design (synopsis and Section 9.1):** Initially, cohorts of approximately 10 subjects will be enrolled sequentially at progressively shorter infusion durations, beginning with the 60-minute infusion duration, progressing down to the 45-minute infusion duration and then to the 30-minute infusion duration. If deemed safe, enrollment will continue in the chosen infusion duration cohort until approximately 110 subjects are enrolled (e.g. targeted 110 subjects in the 30-minute infusion cohort, unless 30-minute infusion is not tolerated, then approximately 110 subjects may be enrolled in the 45-minute or 60-minute infusion cohort).	*Updated targeted number of subjects enrolled.*

Study Design (synopsis and Section 9.1): Enrollment will be paused after the 10th subject of each infusion duration cohort is enrolled until after the 4-week (3-infusion visits) safety assessment analysis results are known and reviewed by Safety Review Committee.	**Study Design (synopsis and Section 9.1):** None.	*Removed – this didn't apply to cohorts beyond initial cohort.*
Study Design (synopsis and Section 9.1): Further, if the Safety Review Committee confirms that the percentage of subjects meeting infusion speed-limiting criteria are less than the thresholds specified in Section 9.2 after approximately 10 subjects receive infusions at the 30-minute infusion duration, then additional subjects will be enrolled.	**Study Design (synopsis and Section 9.1):** Further, if the Safety Review Committee confirms that the percentage of subjects meeting infusion speed-limiting criteria are less than the thresholds specified in Section 9.2 then additional subjects will be enrolled (for a total of approximately 110 subjects in the given cohort).	*Updated targeted number of subjects enrolled.*
Study Design (synopsis and Section 9.1): The Safety Review Committee can increase the number of subjects at the chosen infusion duration level to up to approximately 80 subjects, if they determine that more safety data is needed.	**Study Design (synopsis and Section 9.1):** The Safety Review Committee can modify the number of subjects at the chosen infusion duration level, if they determine that more safety data is needed.	*Updated for clarification.*
Study Design (synopsis and Section 9.1): If any of the safety assessments indicate that a specific infusion duration is not tolerated based on pre-determined criteria, then the study will enroll additional subjects at the previous infusion duration (which is 15 minutes longer than the one at which infusion speed limiting criteria were met). In the event that the initial 60-minute infusion duration is not tolerated based on pre-determined criteria, then the study is terminated.	**Study Design (synopsis and Section 9.1):** If any of the safety assessments indicate that a specific infusion duration is not tolerated based on pre-determined criteria, then the study may enroll additional subjects at a previous infusion duration. In the event that the initial 60-minute infusion duration is not tolerated based on pre-determined criteria, then the study may be revised or terminated (after internal review and assessment).	*Updated for clarification.*
Study Design (synopsis and Section 9.1): An External Adjudication Committee and internal Safety Review Committee (SRC) will be established for this study to adjudicate the AESIs and to review the aggregate safety data. Subject safety and tolerability of the pegloticase regimen will be discussed and the committee will make a recommendation to the Sponsor as whether to continue the current treatment regimen or to modify the assigned treatment regimen. AESIs defined in the protocol (See Section 9.6.1.2.1.5) include IRs, anaphylaxis and cardiovascular events. The AESI of gout flare will not be adjudicated. The Safety Review Committee will be comprised of members of the Horizon Clinical Development and Patient Safety and Pharmacovigilance Teams. External Adjudication committee will be comprised of external experts with experience in immunology, allergic reactions, rheumatology	**Study Design (synopsis and Section 9.1):** An External Adjudication Committee will be established for this study to adjudicate the AESIs. The External Adjudication Committee will be comprised of external experts with experience in immunology, allergic reactions, rheumatology and/or cardiovascular diseases. Details outlining the responsibilities of the Adjudication Committee will be included in the Adjudication Committee charter. AESIs defined in the protocol (See Section 9.6.1.2.1.5) include IRs, anaphylaxis and cardiovascular events. The AESI of gout flare will not be adjudicated. Aggregate safety data will be reviewed by the internal Safety Review Team (SRT) and Safety Review Committee (SRC). Subject safety and tolerability of the pegloticase regimen will be discussed to establish a recommendation as to whether to continue the current treatment regimen or to modify the assigned treatment regimen. The SRC will be comprised of members of the Horizon Clinical Development and Patient Safety	*Clarified responsibilities and expectations of reviews/assessments for each of the committees involved.*

and/or cardiovascular diseases. Meetings will occur at pre-determined timepoints or ad-hoc dependent on any potential safety signals reported (e.g. anaphylaxis or any SAE related to pegloticase infusion). Details outlining the responsibilities of the adjudication committee will be included in the adjudication committee charter.	and Pharmacovigilance Teams. Meetings will occur at pre-determined timepoints or ad-hoc dependent on any potential safety signals reported (e.g. anaphylaxis or any SAE related to pegloticase infusion). If any anaphylaxis event or SAE related to pegloticase infusion occurs with any subject, real-time with expedited review of patient profiles and/or relevant data available in the electronic data capture will occur.	
Study Design: (Schematic) Original Study Schematic Diagram	**Study Design: (Schematic)** Amended Schematic added	*Updated schematic - administrative change (added Week 10 to the list of infusions)*
Study Design (Schematic – Footnote 3): The determination on whether to enroll the next cohort of subjects to a lower infusion duration level will be based on whether the previous cohort meets the Infusion Speed-Limiting Criteria as well as the Safety Review Committee decision. Expansion Cohort may follow Cohort 2 or Cohort 3, depending on tolerability assessment decision.	**Study Design (Schematic – Footnote 3):** The determination on whether to enroll the next cohort of subjects to a different infusion duration level will be based on whether the previous cohort meets the Infusion Speed-Limiting Criteria as well as the Safety Review Committee decision.	*Removed reference to expansion – it's not applicable.*
Dosage Form and Strength Formulation (synopsis and Section 9.5.4): Pegloticase will be supplied as KRYSTEXXA which is commercially available in the United States and will be packaged in sterile, single-use 2-mL glass vials with a Teflon®-coated (latex-free) rubber injection stopper to deliver pegloticase as 8 mg of uricase protein in 1 mL volume.	**Dosage Form and Strength Formulation (synopsis and Section 9.5.4):** Pegloticase will be supplied as KRYSTEXXA which is commercially available in the United States and will be packaged in sterile, single-use 2-mL glass vials with coated (latex-free) rubber injection stopper to deliver pegloticase as 8 mg of uricase protein in 1 mL volume.	*Removed based on the updated USPI.*
Infusion Speed-Limiting Criteria (throughout the protocol): If ≤ one-third of subjects meet infusion speed-limiting criteria at the same infusion duration…	**Infusion Speed-Limiting Criteria (throughout the protocol):** If ≤ one-eighth of subjects meet infusion speed-limiting criteria at the same infusion duration…	*Updated threshold (<12.5%) based on the FDA feedback.*
Infusion Speed-Limiting Criteria (synopsis and Section 9.2): In the event that > one-third of subjects meet infusion-speed limiting criteria at the initial 60-minute infusion duration, then the study is terminated.	**Infusion Speed-Limiting Criteria (synopsis and Section 9.2):** In the event that > one-eighth of subjects meet infusion-speed limiting criteria at the initial 60-minute infusion duration, then the study may be revised or terminated (after internal review and assessment).	*Updated to clarify that further reassessment/revision may be done before the study is terminated.*
Infusion Speed-Limiting Criteria (synopsis and Section 9.2): If any anaphylaxis event or SAE related to pegloticase infusion occurs with any subject, further enrollment and dosing with pegloticase will be suspended pending expedited review of all pertinent data by the Adjudication and Safety Review Committee. An independent	**Infusion Speed-Limiting Criteria (synopsis and Section 9.2):** If any anaphylaxis event or SAE related to pegloticase infusion occurs with any subject, all pertinent data will be provided for expedited review to the Adjudication Committee (for the purpose of adjudicating AESIs) and the SRT/SRC. If any anaphylaxis event or SAE	*Updated to remove redundant information and to clarify the expectations for the review.*

Adjudication Committee will meet on an ad hoc basis to review and assess the event and it will be the responsibility of the Adjudication Committee to make a recommendation to the Sponsor if they believe that enrollment and/or further dosing should be suspended for a specific infusion duration time. Details outlining the responsibilities of the adjudication committee will be included in the adjudication committee charter. If any anaphylaxis event or SAE related to pegloticase infusion occurs with any subject and the Adjudication and Safety Review Committee recommends continuing at the same infusion duration, the next 3 subjects will be enrolled in a sequential manner. Each of the next 3 subjects must complete 3 infusions prior to enrollment of the next subject.	related to pegloticase infusion occurs with any subject, real-time with expedited review of patient profiles and/or relevant data available in the electronic data capture will occur.	
Statistical Analysis on Primary and Secondary Endpoints (throughout the protocol): … one-sided 95% confidence interval…	**Statistical Analysis on Primary and Secondary Endpoints (throughout the protocol):** … two-sided 95% confidence interval…	*Updated based on sample size justification*
Sample Size Estimate (synopsis and Section 9.7.9): Cohorts of approximately 10 subjects will be enrolled sequentially at progressively shorter infusion durations, beginning with the 60-minute infusion duration, progressing down to the 45-minute infusion duration and then to the 30-minute infusion duration. Approximately 60 subjects are planned to be enrolled into the shortest infusion cohort that does not meet the dose limiting criteria. Therefore, the total number of subjects enrolling across the 3 different cohorts in the study is approximately 80. The primary tolerability endpoint, the incidence of subjects experiencing IRs (including anaphylaxis) related to pegloticase from Day 1 to Week 24 Visit, will be demonstrated to be statistically less than 20% (clinically important threshold). If no more than 6/60 (10%) of subjects at the chosen infusion duration are observed to have an IR during the course of the study treatment. In that case, the upper bound of a one-sided 95% confidence interval for the incidence of IRs is 18.8%. The Safety Review Committee may recommend increasing the sample size for the chosen infusion duration by up to 20 subjects, if they believe more safety data are needed. If 80 subjects are enrolled at the chosen infusion duration and 9/80 (11.3%) subjects experience an IR, then the upper bound is 18.9%.	**Sample Size Estimate (synopsis and Section 9.7.9):** Initially, cohorts of approximately 10 subjects will be enrolled sequentially at progressively shorter infusion durations, beginning with the 60-minute infusion duration, progressing down to the 45-minute infusion duration and then to the 30-minute infusion duration. Approximately 110 subjects are planned to be enrolled into the selected cohort. Therefore, the minimum number of subjects enrolling across the 3 different cohorts in the study is approximately 130. Based on the MIRROR-RCT study, we expect approximately 5.0% of subjects to have an IR (including events of anaphylaxis) when taking pegloticase concurrently with MTX. The sample size of 110 for the selected cohort is chosen to ensure a high probability of ruling out an unacceptably high IR rate. If the observed IR rate is 5%, there is a greater than 80% probability that the upper bound of the two-sided 95% exact confidence interval for the IR rate is less than 13%.	*Updated description and justification for the sample size increase to 110 subjects in the shortest infusion duration chosen.*

2.1 Schedule of Assessments (Footnote 1): The Screening Visit can occur up to 35 days prior to Day 1 visit.	**2.1 Schedule of Assessments (Footnote 1):** The Screening Visit can occur up to 35 days prior to Week -4 visit. HbA1c testing is required as part of the Hematology panel during Screening period (refer to Guidance on Blood Glucose Monitoring in Section 9.1).	*Administrative change.* *Updated to include requirement for the HbA1c to be collected during Screening.*
2.1 Schedule of Assessments (Footnote 6 and Section 9.5.9): Prior concomitant medications (not including gout medications) will be collected for 1 year prior to screening.	**2.1 Schedule of Assessments (Footnote 6 and Section 9.5.9):** Prior concomitant medications (not including gout medications) will be collected for 1 year prior to screening (as well as history of COVID-19 vaccinations).	*Updated to include requirements for all historical COVID vaccinations to be captured under con meds.*
9.1 Overall Study Design and Plan None.	**9.1 Overall Study Design and Plan** Guidance on Blood Glucose Monitoring: HbA1c testing must be performed at Screening for all subjects (locally or centrally): If HbA1c >6.5% and/or if subject has known diagnosis of diabetes mellitus, additional measures are recommended: • Investigator asked to closely monitor glucose levels and adjust any diabetic medications as necessary • Subject should consult their primary care physician and/or Endocrinologist managing their diabetes The pre-infusion IV steroid dose may be reduced (e.g., methylprednisolone 75 mg IV) after consulting with the Horizon Medical Monitor.	*Added guidance and instructions on blood glucose monitoring due to potential increased risk of steroid induced hyperglycemia.*
9.5.2.3 Infusion Reaction Prophylaxis None.	**9.5.2.3 Infusion Reaction Prophylaxis** NOTE: If subject's HbA1c is >6.5% at Screening and/or if subject has known diagnosis of diabetes mellitus, the pre-infusion IV steroid dose may be reduced (e.g., methylprednisolone 75 mg IV) after consulting with the Horizon Medical Monitor.	*Added guidance on blood glucose monitoring due to potential increased risk of steroid induced hyperglycemia.*
9.5.8 Method of Assigning Subjects to Treatment Groups Infusion duration assignment may be progressively shortened to 45 minute or 30-minute infusion durations based on tolerability of previous subjects. After the investigator/study site identifies a potential patient, the investigator/study site should notify Sponsor of potential patient by sending a Screening Notification email to the Study Manager and Medical Monitor. Formal screening procedures should not begin until a slot has been confirmed for the potential patient. The sponsor will confirm by email that the patient is held a spot for potential treatment.	**9.5.8 Method of Assigning Subjects to Treatment Groups** Infusion duration assignment may be progressively shortened to 45 minute or 30-minute infusion durations based on tolerability of previous subjects and the infusion duration cohort may be modified based on the safety and tolerability assessments.	*Updated to clarify the expectations for screening and treatment assignment.*

9.6.1.4 Medical/Surgical History None.	**9.4.1.4 Medical/Surgical History** For subjects with reported allergic history (e.g., seasonal allergies, food allergies, allergies to medications) the Investigator/site should collect additional supplemental information (e.g., severity, current status etc.). In the event of multiple allergies and/or moderate to severe (Grade 2 or higher) allergic history the Investigator should consult with the Medical Monitor prior to enrolling the subject.	*Updated guidance to minimize the risk of potential IRs (patients with severe history of allergies may have a higher chance of IR/Anaphylaxis occurrence).*
9.7.2 Analysis Sets None.	**9.7.2 Analysis Sets** • Safety set: all subjects who receive at least 1 dose of pegloticase.	*Updated analysis set list.*
9.7.5 Endpoint Analysis All analyses will be performed using the mITT set. Baseline characteristics and safety relating to only the MTX Run-in period will be summarized for the ITT set.	**9.7.5 Endpoint Analysis** All efficacy analyses will be performed using the mITT set. Baseline characteristics and safety relating to only the MTX Run-in period will be summarized for the ITT set and/or mITT set. All safety analyses relating to pegloticase + MTX period will be summarized using the safety set.	*Clarified analysis sets to be used for specific analyses.*
9.7.8 Interim Analysis • After 15 subjects complete at least 3 infusions at one assigned infusion duration level. • After 20 subjects complete at least 3 infusions at one assigned infusion duration level. • After all subjects complete at least 3 infusions. • After all subjects complete at least 6 infusions.	**9.7.8 Interim Analysis** • After 15 subjects complete at least 3 infusions at one assigned infusion duration level if applicable. • After 20 subjects complete at least 3 infusions at one assigned infusion duration level if applicable. • After all subjects complete at least 3 infusions.	*Updated to clarify the safety data analysis expectations.*

2 SYNOPSIS

Protocol Title: A Phase 4, Multicenter, Open-Label, Infusion Duration Study To Assess Safety, Tolerability and Efficacy of Pegloticase Administered With a Shorter Infusion Duration in Subjects with Uncontrolled Gout Receiving Methotrexate	
Protocol Number: HZNP-KRY-403	**Phase**: 4
Protocol Version: 5.0	
Test Drugs: KRYSTEXXA (pegloticase)	**Indication**: Chronic gout refractory to conventional therapy in adult patients
Number and Country of Study Sites: Approximately 40 study centers in the United States	

Objectives:

The overall objective of this study is to assess the safety, tolerability and efficacy of pegloticase administered with a shorter infusion duration in subjects with uncontrolled gout receiving methotrexate.

Primary Objective

The primary objective is to assess the tolerability of pegloticase infusions administered with methotrexate (MTX) from Day 1 through Week 24 in the cohort chosen to be the most desirable duration for infusion, as measured by the incidence of infusion reactions (including anaphylaxis) related to pegloticase.

Secondary Objectives

The secondary objectives will be assessed for the cohort chosen to be the most desirable duration for infusion and include:

- Estimate the response rate at Month 6 (Weeks 20, 22 and 24), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 6.
- Assess the proportion of subjects receiving pegloticase with MTX who experienced any of the following events: infusion reaction (IR) leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria.
- Assess the time to any of the following events: IR leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria (two consecutive pre-infusion sUAs > 6 mg/dL).

Exploratory Objectives

[redacted]

[redacted]

- Assess the pharmacokinetics of pegloticase.
- Assess the profile of anti-uricase antibodies and anti-poly (ethylene glycol) antibodies.

Safety Objectives

- Assess the incidence of adverse events of special interest (AESI), including IRs, anaphylaxis, gout flares, cardiovascular events and the AE/SAE profile overall.
- Assess the proportion of subjects who experienced IR leading to slowing down of the infusion rate or discontinuation of treatment.
- Assess the time to first IR leading to slowing down of the infusion rate or discontinuation of treatment.
- Assess the time to first IR.
- Assess the proportion of subjects who were able to complete all infusions over the assigned treatment duration length or a lesser time, without clinically requiring an increased infusion time.
- Assess the proportion of infusions completed over the assigned duration length or a lesser time, without clinically requiring an increased infusion time.
- Laboratory tests and 12-lead electrocardiogram (ECG).
- Vital signs and physical examinations.

Study Design:

This is a Phase 4, multicenter, open-label, infusion duration study of pegloticase administered over <120 minutes in combination with MTX to evaluate the safety, tolerability, and efficacy in treating adult subjects with uncontrolled gout. Approximately 10 subjects in each cohort are planned to be enrolled initially. If deemed safe, an additional 100 subjects to be enrolled in the selected cohort in order to have approximately 110 subjects exposed. Treatment duration with pegloticase will be approximately 24 weeks.

The study design will include: 1) a Screening Period, lasting up to 35 days; 2) a 4-week MTX Run-in Period; 3) a 24-week Pegloticase + MTX Period which includes an End-of study Week 24/Early Termination Visit; 4) a safety Follow-up Phone/Email 30 days after the last pegloticase infusion and 5); a 3-month Post-Treatment Follow-up.

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

Subjects will also take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) continuing until prior to the End of Pegloticase Infusion Visit (if applicable) or the

Week 24/End of Study/Early Termination Visit.

Subjects must be able to tolerate MTX at a dose of 15 mg during the 4-week MTX Run-in Period (prior to Day 1) to be eligible to participate in the Pegloticase + MTX Period. Subjects who are unable to tolerate MTX at a dose of 15 mg during the MTX Run-in Period will be considered screen failures.

Female subjects who take at least one dose of MTX and who are females of childbearing potential, will receive a safety Follow-up phone call/e-mail approximately 30 days after the last dose of MTX to verify at least one ovulatory cycle has occurred after the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. For those subjects who take at least one dose of MTX and who are non-vasectomized males an inquiry will be conducted at the Post-Treatment 3-month Follow-up visit (or 3 months after the subject's last dose of MTX) after MTX discontinuation regarding partner pregnancy.

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

Prior to the Treatment Period, subjects will begin taking at least one of the per protocol standard gout flare prophylaxis regimen (colchicine 0.6 mg/day and/or nonsteroidal anti-inflammatory drug (NSAID) and/or low dose prednisone <10 mg/day) for ≥1 week before the first dose of pegloticase and continues flare prophylaxis throughout the pegloticase treatment period per American College of Rheumatology guidelines [Khanna D et al. 2012].

For IR prophylaxis, fexofenadine (180 mg orally) will be taken the night before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) over an infusion duration between 10 and 30 minutes, will be administered immediately prior to each infusion.

During the Pegloticase + MTX Period, all subjects will receive pegloticase 8 mg every 2 weeks administered IV for a total of 12 infusions from Day 1 through Week 22, inclusive.

Up to three pegloticase infusion durations will be assessed in the Pegloticase + MTX Period: 60-minute infusion, 45-minute infusion and 30-minute infusion. Initially, cohorts of approximately 10 subjects will be enrolled sequentially at progressively shorter infusion durations, beginning with the 60-minute infusion duration, progressing down to the 45-minute infusion duration and then to the 30-minute infusion duration. If deemed safe, enrollment will continue in the chosen infusion duration cohort until approximately 110 subjects are enrolled (e.g. targeted 110 subjects in the 30-minute infusion cohort, unless 30-minute infusion is not tolerated, then approximately 110 subjects may be enrolled in the 45-minute or 60-minute infusion cohort). The most desirable infusion duration is the shortest duration, which is shown to be safe and well tolerated.

After the first 3 subjects at each infusion duration complete at least 4 weeks of the Pegloticase + MTX period (3 infusion visits), a holistic safety assessment will be performed by the internal Safety Review Committee on available subjects' data. Study enrollment will not be paused. If a subject discontinues treatment or study prior to the third infusion visit, their available data is still included in the safety assessment. If the safety assessment

indicates that the infusion duration is well tolerated (based on pre-determined infusion speed-limiting criteria as described in Section 9.2), then additional safety assessments will continue to be performed based on available subjects' data after 6 subjects and 10 subjects complete at least 4 weeks of the Pegloticase + MTX period (3 infusion visits).

If the Safety Review Committee confirms that the percentage of subjects meeting infusion speed-limiting criteria are less than the thresholds specified in Section 9.2, then enrollment of subjects at the next progressively shorter infusion duration cohort (15 minutes shorter duration) will begin. Further, if the Safety Review Committee confirms that the percentage of subjects meeting infusion speed-limiting criteria are less than the thresholds specified in Section 9.2 then additional subjects will be enrolled (for a total of approximately 110 subjects in the given cohort).

If any of the safety assessments indicate that a specific infusion duration is not tolerated based on pre-determined criteria, then the study may enroll additional subjects at a previous infusion duration. In the event that the initial 60-minute infusion duration is not tolerated based on pre-determined criteria, then the study may be revised or terminated (after internal review and assessments).

If > 10 subjects are enrolled at any infusion duration, additional safety assessments will be performed when 15 subjects and 20 subjects complete at least 4 weeks of the Pegloticase + MTX period (3 infusion visits). Once all subjects complete at least 4 weeks of the Pegloticase + MTX period (3 infusion visits), additional safety assessments will be done as needed (refer to the Safety Review Committee charter). If a subject discontinues treatment or study prior to either of these time-points, their available data is still included in the safety assessment.

The Safety Review Committee can modify the number of subjects at the chosen infusion duration, if they determine that more safety data is needed.

Investigators will be permitted to adjust the duration of the infusion at a particular infusion visit regardless of initial treatment duration assignment, if needed. The decision to modify the infusion duration at a visit will be allowed based on the investigator's discretion. Subjects may return to the original infusion duration for subsequent infusions.

Pegloticase will be administered after all pre-dose study visit assessments have been completed at each visit. The date and time of infusion start and stop will be recorded.

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

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

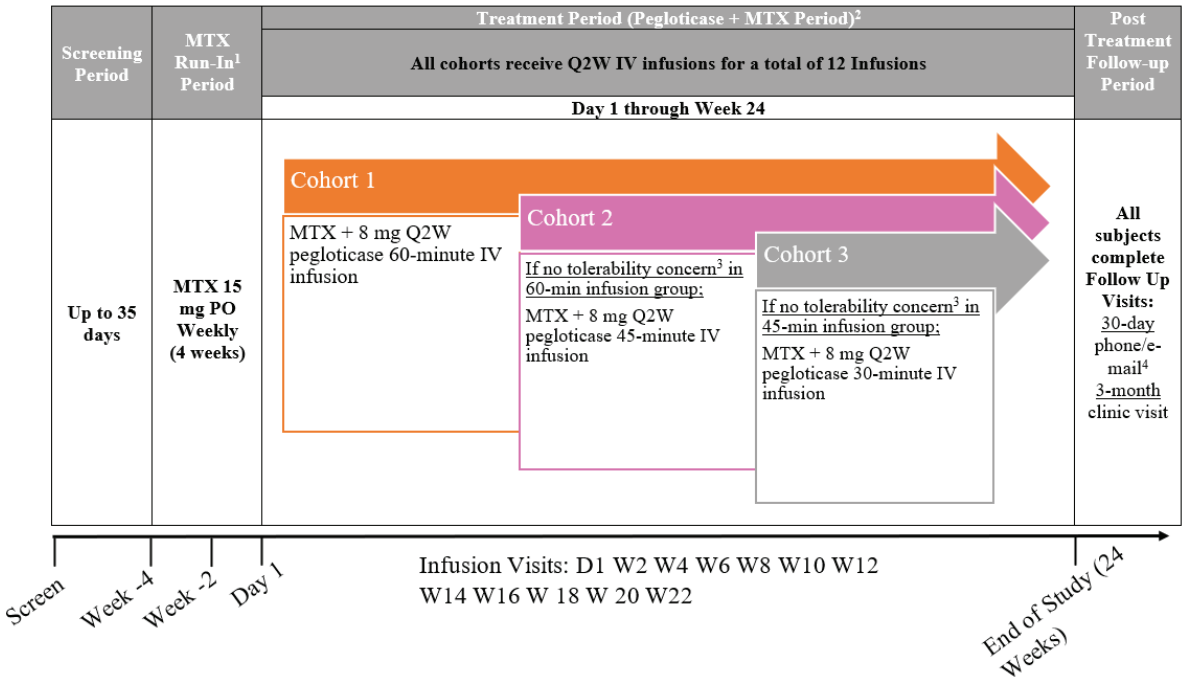
The total blood volume to be collected from each subject during this study is approximately 450 mL.

An External Adjudication Committee will be established for this study to adjudicate the AESIs. The External Adjudication Committee will be comprised of external experts with experience in immunology, allergic reactions, rheumatology and/or cardiovascular diseases. Details outlining the responsibilities of the Adjudication Committee will be included in the Adjudication Committee charter. AESIs defined in the protocol (See Section 9.6.1.2.1.5) include IRs, anaphylaxis and cardiovascular events. The AESI of gout flare will not be adjudicated.

Aggregate safety data will be reviewed by the internal Safety Review Team (SRT) and Safety Review Committee (SRC). Subject safety and tolerability of the pegloticase regimen will be discussed to establish a recommendation as to whether to continue the current treatment regimen or to modify the assigned treatment regimen.

The SRC will be comprised of members of the Horizon Clinical Development and Patient Safety and Pharmacovigilance Teams. Meetings will occur at pre-determined timepoints or ad-hoc dependent on any potential safety signals reported (e.g. anaphylaxis or any SAE related to pegloticase infusion). If any anaphylaxis event or SAE related to pegloticase infusion occurs with any subject, real-time with expedited review of patient profiles and/or relevant data available in the electronic data capture will occur.

Study Design (continued):



IV = intravenous; MTX = methotrexate; PO = oral; Q2W = every 2 weeks; W = week
Note: Study visits must be completed within ±3 days of the target visit date.

1. Prior to the Treatment Period, subjects will begin taking at least one of the per protocol standard gout flare prophylaxis regimen (colchicine 0.6 mg/day and/or NSAID and/or low dose prednisone <10 mg/day) for ≥1 week before the first dose of pegloticase and continuing flare prophylaxis throughout the pegloticase treatment period per American College of Rheumatology guidelines. For IR prophylaxis, fexofenadine (180 mg orally) will be taken the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) over an infusion duration between 10 and 30 minutes, will be administered immediately prior to each infusion.
2. Stopping rules will be implemented: Subjects with 2 sUA levels > 6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue from pegloticase therapy and complete the End of Pegloticase Infusions Visit and remain on study.
3. The determination on whether to enroll the next cohort of subjects to a different infusion duration level will be based on whether the previous cohort meets the Infusion Speed-Limiting Criteria as well as the Safety Review Committee decision.
4. All subjects will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of pegloticase to assess if any SAEs have occurred. If the subject discontinues treatment but continues in the study, then this follow-up visit may be replaced by a scheduled study visit.

Subject Population:

Subjects diagnosed with gout eligible for this study will have sUA ≥6 mg/dL and inability to maintain sUA <6 mg/dL on other urate lowering therapy, or intolerable side effects associated with current urate-lowering therapy, or with a contraindication to xanthine oxidase inhibitor therapy.

Inclusion Criteria:

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

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

with the initiation of MTX at Week -4 and continuing through 3-Month Post-Treatment Follow-up.

8. Able to tolerate MTX 15 mg for 4 weeks during the MTX Run-in Period prior to the first dose of pegloticase.

Exclusion Criteria:

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

1. Weight >160 kg (352 pounds) at Screening.
2. Any serious acute bacterial infection, unless treated and completely resolved with antibiotics at least 2 weeks prior to Week -4 Visit.
3. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis.
4. Current or chronic treatment with systemic immunosuppressive agents such as MTX, azathioprine, or mycophenolate mofetil; prednisone ≥10 mg/day or equivalent dose of other corticosteroid on a chronic basis (defined as 3 months or longer) would also meet exclusion criteria.
5. Known history of any solid organ transplant surgery requiring maintenance Immunosuppressive therapy unless treated and no chronic or active infection confirmed by HBV serology.
6. Known history of hepatitis B virus surface antigen positivity or hepatitis B DNA positivity, unless treated and viral load is negative and no chronic or active infection confirmed by HBV serology.
7. Known history of hepatitis C virus RNA positivity unless treated and viral load is negative.
8. Known history of Human Immunodeficiency Virus (HIV) positivity.
9. Glucose-6-phosphate dehydrogenase (G6PD) deficiency (tested at Screening Visit).
10. Severe chronic renal impairment (estimated glomerular filtration rate <40 mL/min/1.73 m^2) at the Screening Visit based on 4 variable-Modification of Diet in Renal Disease [MDRD] formula or currently on dialysis.
11. Non-compensated congestive heart failure or hospitalization for congestive heart failure or treatment for acute coronary syndrome (myocardial infarction or unstable angina) within 3 months of the Screening Visit, or current uncontrolled arrhythmia, or current uncontrolled blood pressure (BP) (>160/100 mmHg) prior to Week -4.
12. Pregnant, planning to become pregnant, breastfeeding, planning to impregnate female partner, or not on an effective form of birth control, as determined by the Investigator.
13. Prior treatment with pegloticase (KRYSTEXXA), another recombinant uricase (rasburicase), or concomitant therapy with a polyethylene glycol-conjugated drug.

14. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product.
15. Contraindication to methotrexate (MTX) treatment or MTX treatment considered inappropriate.
16. Known intolerance to MTX.
17. Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to MTX administration at Week -4, or plans to take an investigational drug during the study.
18. Liver transaminase levels (AST or ALT) > upper limit of normal (ULN) or albumin < the lower limit of normal (LLN) at the Screening Visit.
19. Chronic liver disease.
20. White blood cell count < 4,000/ul, hematocrit < 32 percent, or platelet count <75,000/ul.
21. Currently receiving systemic or radiologic treatment for ongoing cancer.
22. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix.
23. Uncontrolled hyperglycemia with a plasma glucose value >240 mg/dL at Screening that is not subsequently controlled by the end of the Screening.
24. Diagnosis of osteomyelitis.
25. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
26. 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.
27. Alcohol use in excess of 3 alcoholic beverages per week.
28. A known intolerance to all protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤10 mg/day).
29. Currently receiving urate-lowering therapies and unable to discontinue treatment at least 7 days prior to MTX dosing at Week -4 and remain off of urate lowering therapy when receiving pegloticase infusions during the study.
30. Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest X-ray may be performed during Screening.

Dose Regimen/Route of Administration:

MTX:

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

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

During the MTX Run-in Period, if a dose is missed, it should be taken as soon as it is remembered. If it is within 48 hours of the next scheduled dose, the subject will be instructed to skip the missed dose and resume at the next regularly scheduled time; thus, subjects will be instructed not to double a dose to make up for a missed dose if within 48 hours of the next dose. Investigators may choose to have subjects take the weekly dose divided over the day (i.e. BID, TID).

During the Pegloticase + MTX Period, MTX should be taken 1 to 3 days prior to the pegloticase infusion and one additional weekly dose after the last infusion (at Week 22) for subjects who have not stopped pegloticase due to study sUA Discontinuation Criteria. If a subject is not able to take the MTX 1 to 3 days prior to the pegloticase infusion, MTX must be taken ≥60 minutes prior to the pegloticase infusion.

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

Subjects will also take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the Week 24 Visit.

Pegloticase:

All subjects who meet the inclusion/exclusion criteria and tolerate oral MTX 15 mg weekly during the MTX Run-in Period will receive pegloticase at a dose of 8 mg administered IV every 2 weeks for a total of 12 infusions from Day 1 through Week 22 inclusive (Pegloticase + MTX Period). The date and start and stop time of infusion will be recorded. Subjects will not be fasting on the day of infusion and will be encouraged to have a snack or normal meal before or after the infusion.

All subjects will receive standardized prophylactic treatment to reduce the risk of acute gout flares, beginning ≥1 week before the first dose of pegloticase and continuing throughout the pegloticase treatment per American College of Rheumatology guidelines [Khanna D et al. 2012].

Standardized IR prophylaxis consisting of pre-treatment with an antihistamine, acetaminophen and a corticosteroid will accompany each infusion.

Dosage Form and Strength Formulation (Pegloticase and MTX):

Pegloticase will be supplied as KRYSTEXXA which is commercially available in the United States and will be packaged in sterile, single-use 2-mL glass vials with coated (latex-free)

rubber injection stopper to deliver pegloticase as 8 mg of uricase protein in 1 mL volume. Pegloticase will be administered as an admixture of 8 mg in 50 mL of 0.45% or 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump.

An alternative presentation of pegloticase is filled into sterile, single-use 50-mL glass vials with a Fluorotec-coated rubber injection stopper which delivers 8 mg uricase in a 50 mL ready-to-use solution.

Pegloticase will not be administered as an IV push or bolus.

MTX 2.5 mg tablets for oral administration will be provided to all subjects as a commercially available generic.

Duration of Treatment and Follow-up:

Screening: Up to 35 days prior to the Pegloticase + MTX Period.

MTX Run-in Period (Week – 4 to Day 1): 4 weeks of MTX dosing prior to initial pegloticase dose.

Pegloticase + MTX Period (Day 1 through Week 24): 24 weeks (infusion visits every 2 weeks) plus the End-of study/Early Termination Visit (Week 24)

Week 24/End-of-study/Early Termination Visit: Week 24 or earlier if the subject withdraws consent to participate in the study.

End of Pegloticase Infusions Visit (if applicable): If the subject discontinues pegloticase treatment prior to infusion Week 22, such as due to the sUA Discontinuation Criteria, the subject will complete this visit within approximately 2 weeks of the last infusion. Subjects will continue in study for Follow-Up visits, including the 30-day Follow-Up Email/Phone call, Week 24/End of Study/Early Termination and 3 Month Post-Treatment Follow-up Visits.

Safety Follow-up Visit: All subjects will receive a safety Follow-up phone call/e-mail/visit approximately 30 days after the last dose of pegloticase to assess if any AE/SAE's have occurred and to confirm if any previous AE/SAEs have resolved. Subjects who receive at least one dose of MTX and are females of childbearing potential, will receive a safety Follow-up phone call/e-mail/ approximately 30 days after the last dose of MTX to verify at least one ovulatory cycle has occurred after the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. Subjects who receive at least one dose of MTX and are non-vasectomized males, a phone/e-mail/site visit inquiry will be conducted 3 months after MTX discontinuation regarding partner pregnancy (inquiry can occur during the 3-month Post-Treatment Follow-up). If the subject discontinues treatment but continues in the study, then this Follow-up visit may be replaced by a scheduled study visit.

3-Month Post-Treatment Follow-up Visit: All subjects will be followed for a minimum of 3 months following the last infusion, with follow-up after Week 24 as warranted.

Restricted Medications

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

The following medications are prohibited during the study:

- Concomitant therapy with allopurinol, febuxostat or other urate lowering medications or a polyethylene glycol-conjugated drug
- Systemic or radiologic treatment for ongoing cancer, excluding non-melanoma skin cancer
- Current or chronic treatment with systemic Immunosuppressive agents

Removal of Subjects from Treatment or Assessment

Every effort should be made to retain a subject in the study to monitor their safety. However, subjects may withdraw consent or discontinue treatment or participation from the study at any time, without prejudice to further treatment. In addition, the Investigator may terminate a subject's treatment at any time. The primary reason for discontinuation from the study and/or study drug should be recorded on the eCRF.

Criteria for Evaluation:

Safety and tolerability assessments will include monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations, 12-lead ECG and monitoring of hematology and blood chemistry.

Efficacy will be assessed by sUA levels.

The incidence of anti-uricase and anti-polyethylene glycol antibodies will be assessed at specified time points.

Infusion Speed-Limiting Criteria:

Infusion speed-limiting criteria will be met if a subject experiences any severe (Grade ≥3) IRs or any other severe AEs within 24 hours of receiving pegloticase infusion and attributed to the infusion and not any other underlying disease process. The signs and symptoms of the severe IRs are usually prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion) or recurrent following initial improvement. Possible associated signs and symptoms of IRs may include but not limited to:

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

If ≤ one-eighth of subjects meet infusion speed-limiting criteria at the same infusion duration after 3 subjects and after 6 subjects, then enrollment may continue at the same infusion

duration. If ≤ one-eighth of subjects meet infusion speed-limiting criteria at the same infusion duration after 10 subjects, then enrollment may continue at the next progressively shorter infusion duration.

If > one-eighth of subjects meet infusion speed-limiting criteria, then enrollment at that infusion duration may be suspended. The Safety Review Committee must confirm that infusion speed-limiting criteria were met, prior to additional patients being enrolled.. In the event that > one-eighth of subjects meet infusion-speed limiting criteria at the initial 60-minute infusion duration, then the study may be revised or terminated (after internal review and assessment).

If an anaphylaxis event occurs in any subject, further dosing with pegloticase for that subject will be terminated.

If any anaphylaxis event or SAE related to pegloticase infusion occurs with any subject, all pertinent data will be provided for expedited review to the Adjudication Committee (for the purpose of adjudicating AESIs) and the SRT/SRC. If any anaphylaxis event or SAE related to pegloticase infusion occurs with any subject, real-time with expedited review of patient profiles and/or relevant data available in the electronic data capture will occur.

Individual Subject sUA Discontinuation Criteria:

Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue treatment, but continue on study as described in Section 9.4.3.

Note: The sUA Discontinuation Criteria only pertain to individual subjects and are not sUA Discontinuation Criteria for a group or specific infusion duration.

Statistical Analyses:

Primary Endpoint

The primary endpoint is the incidence of subjects experiencing IRs (including anaphylaxis) related to pegloticase from Day 1 to Week 24 in the cohort chosen to be the most desirable duration for infusion.

Secondary Endpoints

The secondary endpoints will be assessed for the cohort chosen to be the most desirable duration for infusion and include:

- The proportion of Month 6 (Weeks 20, 22 and 24) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.
- The proportion of subjects who experienced any of the following events: IR leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria.
- Time to any of the following events: IR leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria (two consecutive pre-infusion sUAs > 6 mg/dL).

Exploratory Endpoints

[redacted]

Pharmacokinetic and Anti-drug Antibody Endpoints

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

Safety Endpoints

- Incidence of IRs, anaphylaxis, gout flares, cardiovascular events and the AE/SAE profile overall and potentially attributed to the combination of pegloticase and MTX.
- The proportion of subjects who experienced IR leading to slowing down of the infusion rate or discontinuation of treatment.
- The time to first IR leading to slowing down of the infusion rate or discontinuation of treatment.
- Time to first IR.
- The proportion of subjects who were able to complete all infusions over the assigned treatment duration length or a lesser time, without clinically requiring an increased infusion time
- The proportion of infusions completed over the assigned duration length or a lesser time, without clinically requiring an increased infusion time.
- Laboratory tests
- Vital signs & physical examinations

Statistical Analysis on Primary and Secondary Endpoints

The primary analysis will be performed using the modified intention-to-treat (mITT) population, defined as all enrolled subjects who received ≥1 dose of pegloticase. The primary endpoint is the incidence of subjects experiencing an IR (including anaphylaxis) related to pegloticase from Day 1 to Week 24 in the cohort chosen to be the most desirable duration for infusion (e.g. this may be the 30-minute infusion cohort if infusion-speed limiting criteria not met). This endpoint will be analyzed with a summary of the incidence and the corresponding two-sided 95% confidence interval. Additionally, this endpoint will be analyzed for each of the other infusion duration cohorts.

The proportion of responders during Month 6 will be summarized, along with a two-sided 95% exact (Clopper-Pearson) confidence interval for the proportion. A responder is defined as a subject for whom the proportion of time that the sUA-time curve is <6 mg/dL during Month 6 (Weeks 20, 22 and 24) is at least 80%. The proportion of time that the sUA level is below 6 mg/dL is defined as the ratio of the time during which the sUA level remains below 6 mg/dL (using linear interpolation, if necessary) to the entire time interval during Month 6. The proportion of subjects experiencing any of the following events: IR leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria will be presented. This composite endpoint, each individual component of the composite and the proportion of subjects who experienced an IR leading to the slowing down of the infusion rate or discontinuation of treatment will be analyzed for each infusion duration regimen with a summary of the incidence and the corresponding two-sided 95% confidence interval.

Time to subjects meeting any of the composite endpoint criteria will be assessed by assigned treatment regimen. Kaplan-Meier (KM) estimates of the time to event will be presented, along with the corresponding quartiles and two-sided 95% CI for the median time if there are sufficient number of events to perform the analysis. The individual components of the composite endpoint, the time to first IR leading to slowing down of the infusion rate, time to first IR and time to first instance of IR leading to slowing down of the infusion rate or discontinuation of treatment will be summarized in the same way as the composite.

Sample Size Estimate:

Initially, cohorts of approximately 10 subjects will be enrolled sequentially at progressively shorter infusion durations, beginning with the 60-minute infusion duration, progressing down to the 45-minute infusion duration and then to the 30-minute infusion duration. Approximately 110 subjects are planned to be enrolled into the selected cohort. Therefore, the minimum number of subjects enrolling across the 3 different cohorts in the study is approximately 130.

Based on the MIRROR-RCT study (NCT03994731), approximately 5.0% of subjects are expected to have an IR (including events of anaphylaxis) when taking pegloticase concurrently with MTX. The sample size of 110 for the selected cohort is chosen to ensure a high probability of ruling out an unacceptably high IR rate. If the observed IR rate is 5%, there is a greater than 80% probability that the upper bound of the two-sided 95% exact confidence interval for the IR rate is less than 13%.

2.1 Schedule of Assessments

Study Procedure/ Assessment	Screening	MTX Tolerability Assessment Period/ Run-in Period[2]		Pegloticase + MTX Period[4] Day 1 through Week 24												End of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-study/ Early Term.	Safety Follow-up Phone/ Email [25]	Post Treatment Follow-Up[23]
	Screening Visit[1] (35 d)	Week - 4 (±3 d)	Week - 2 (±3 d)	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
				Day 1	2	4	6	8	10	12	14	16	18	20	22				
Pegloticase infusion				Inf 1	Inf 2	Inf 3	Inf 4	Inf 5	Inf 6	Inf 7	Inf 8	Inf 9	Inf 10	Inf 11	Inf 12				
Informed consent	X																		
Enrollment				X															
Demographic data	X																		
Inclusion/ exclusion criteria	X	X		X															
Medical/Surgical History[5]	X																		

Study Procedure/ Assessment	Screening	MTX Tolerability Assessment Period/ Run-in Period[2]		Pegloticase + MTX Period[4] Day 1 through Week 24												End of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-study/ Early Term.	Safety Follow-up Phone/ Email [25]	Post Treatment Follow-Up[23]
	Screening Visit[1] (35 d)	Week - 4 (±3 d)	Week - 2 (±3 d)	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
				Day 1	2	4	6	8	10	12	14	16	18	20	22				
Medication/substance use history[6]	X																		
Physical examination[7]	X	X	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	X		X
Electrocardiogram[9]	X																		
AE/SAE Assessment[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Principle Investigator Assessment of gout flares and intensity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Study Procedure/ Assessment	Screening	MTX Tolerability Assessment Period/ Run-in Period[2]		Pegloticase + MTX Period[4] Day 1 through Week 24												End of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-study/ Early Term.	Safety Follow-up Phone/ Email [25]	Post Treatment Follow-Up[23]
	Screening Visit[1] (35 d)	Week - 4 (±3 d)	Week - 2 (±3 d)	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
				Day 1	2	4	6	8	10	12	14	16	18	20	22				
[redacted]																			
MTX dosing calendar		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
MTX dispensed[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
MTX dosing[12]		Once weekly from Week -4 to Week 23, one week after the Week 22 Visit, inclusive																	
Gout prophylaxis Rxs filled[13]			Rxs filled as needed, start taking at least one protocol standard gout flare prophylaxis regimen ≥1 week before first dose of pegloticase.																
Fexofenadine Rx filled[14]				Rxs filled as needed, first dose of fexofenadine must be taken the day before D1; and in the morning or just prior to each infusion.															
Folic Acid Rx filled[15]		Rxs filled as needed, 1 mg orally every day beginning at Week -4.																	

Study Procedure/ Assessment	Screening	MTX Tolerability Assessment Period/ Run-in Period[2]		Pegloticase + MTX Period[4] Day 1 through Week 24												End of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-study/ Early Term.	Safety Follow-up Phone/ Email [25]	Post Treatment Follow-Up[23]
	Screening Visit[1] (35 d)	Week - 4 (±3 d)	Week - 2 (±3 d)	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
				Day 1	2	4	6	8	10	12	14	16	18	20	22				
IR prophylaxis[16]				X	X	X	X	X	X	X	X	X	X	X	X				
IR Rx prophylaxis compliance check (Yes/No)				X	X	X	X	X	X	X	X	X	X	X	X				
Gout flare prophylaxis compliance check (Yes/No)			X	X	X	X	X	X	X	X	X	X	X	X	X				
Pre-infusion MTX Polyglutamate sampling				X							X				X	X	X		
Pegloticase PK sampling[17]				X	X		X			X				X			X		
sUA[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology [1]	X[1]		X	X	X		X				X				X	X	X		X

Study Procedure/ Assessment	Screening	MTX Tolerability Assessment Period/ Run-in Period[2]		Pegloticase + MTX Period[4] Day 1 through Week 24												End of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-study/ Early Term.	Safety Follow-up Phone/ Email [25]	Post Treatment Follow-Up[23]
	Screening Visit[1] (35 d)	Week - 4 (±3 d)	Week - 2 (±3 d)	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
				Day 1	2	4	6	8	10	12	14	16	18	20	22				
Chemistry	X		X	X	X		X				X				X	X	X		X
Urine Albumin: Creatinine Ratio[22]	X			X	X		X				X				X	X	X		
Antibody testing[19]				X	X		X			X				X			X		X
C-Reactive Protein				X							X						X		
G6PD	X																		
Serum Pregnancy Test[20]	X																X		
Urine Pregnancy test[21]		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
Partner pregnancy[24]																			X

Abbreviations: AE = adverse event; d = day(s); G6PD = glucose-6-phosphate dehydrogenase; 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 Week -4 visit HbA1c testing is required as part of the Hematology panel during Screening period (refer to Guidance on Blood Glucose Monitoring in Section 9.1).
2. During the MTX Tolerability Assessment Period (starting at Week -4 to Day 1), all subjects will take MTX 15 mg orally weekly. The subject must tolerate MTX 15 mg dose during MTX Run in Period to enroll into the Pegloticase + MTX Period. If a subject does not tolerate the MTX 15 mg dose during the Pegloticase + MTX Period, MTX may be dose-reduced after discussion with the Sponsor medical monitor. The subject should remain in the study.
3. Subjects who end treatment due to the sUA Discontinuation Criteria or other reasons should complete the End of Pegloticase Infusions Visit within 2 weeks of the last infusion. Subjects will also complete all regularly scheduled Follow-Up visits including the 30-day Follow-up email/phone call, Week 24/End of Study/Early Termination and 3 Month Post-Treatment Follow-up Visits.
4. 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 Individual Subject sUA Discontinuation Criteria or discontinue treatment for any other reason will enter the off-treatment observation period. During the off-treatment observation period, subjects will return for scheduled visits according to section 9.4.3.
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 (as well as history of COVID-19 vaccinations).
7. A complete physical examination will be performed at the Screening Visit, including assessment of HEENT, heart, lungs, abdomen, skin, extremities and neurological status and musculoskeletal including an assessment for the presence of tophi, as well as gout history and symptom severity. Physical examination findings at screening should be recorded on the medical and surgical history eCRF. A targeted physical examination (for assessment of AEs) will be conducted based on potential risk for or occurrence of AEs at Week -4, Week -2, Day 1 and prior to administration of infusion at Weeks 4, 8, 12, 16, 20, End of Pegloticase Infusions Visit (if applicable), 24/End of Study/Early Termination Visits and 3-Month Follow-Up. Clinically significant findings from the targeted physical examinations will be recorded as AEs.
8. Routine vital signs, including BP, respiratory rate, temperature and heart rate will be measured at Screening, Week -4, Week -2 and at all infusion visits during the Pegloticase + MTX Period and the End of Pegloticase Infusions Visit (if applicable), Week 24/End of Study/Early Termination and 3-month Post-Treatment Follow-up Visit. 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. Subjects arm should be supported at heart level; and cuff placed on the bare arm. A large cuff should be used as needed to fit the upper arm and a consistent arm is to be used at each study visit. The Korotkoff phase V will be used to determine

diastolic BP. During the Pegloticase + MTX Period study visits, vitals should be taken before the pegloticase infusion and any time after the end of the infusion, but prior to subject's discharge/release from the site. When possible, the same staff member should take all BP measurements for a given subject. Weight should be measured in kilograms or pounds without shoes and recorded at the Screening Visit and prior to dosing MTX Week -4 Visit; prior to pegloticase infusion on Day 1 and at the Weeks 8, 16 and at the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 24/End of Study/Early Termination and Month 3 Post-Treatment Follow-up Visits. Height will be collected at the Screening Visit only.

9. Electrocardiogram should be completed at Screening Visit, during the study per investigator discretion and during any potential or suspected IR.

10. AEs/SAEs will be collected from the signature of the ICF through the 3-month Post-Treatment Follow-up visit.

11. MTX tablets will be dispensed and brought back at each visit to check compliance. MTX bottles are 36 count and bottles should be re-dispensed when appropriate. New bottles should not be given at each visit. If subjects require a MTX dose reduction, the Investigator will prescribe the subject the number of tablets to take weekly. The updated number of tablets along with the date and time of each MTX dose should be recorded in the dosing calendar.

12. 15mg of MTX should be taken 1 to 3 days prior to pegloticase infusion; however, if a subject does not do so, MTX must be taken ≥60 minutes prior to pegloticase infusion.

13. It is required that before a subject begins the pegloticase + MTX Period, he or she has been taking at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low dose prednisone <10 mg/day) for ≥1 week before the first dose of pegloticase and continuing throughout the pegloticase treatment period per American College of Rheumatology guidelines [Khanna D et al. 2012].

14. Fexofenadine (180 mg orally) will be taken the day before and the morning or just prior to each infusion. Prescriptions are to be filled at a local pharmacy, as needed.

15. Subjects will take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the End of Pegloticase Infusions Visit (if applicable) or the Week 24/End of Study/Early Termination. Prescriptions are to be filled at a local pharmacy, as needed.

16. IR prophylaxis: fexofenadine (180 mg orally) administered the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) administered on the morning of each infusion; and methylprednisolone (125 mg IV) will be administered over an infusion duration between 10 – 30 minutes, immediately prior to each pegloticase infusion.

17. 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 infusion at the Weeks 2, 6, 12, 20. An additional PK sample will be collected at Week 24 End of Study/Early Termination Visits.

18. Serum samples for measurement of sUA levels will be collected at the Screening Visit, the Week -4 Visit and the Week -2 Visit during the Run-in Period; within 48 hours prior to each pegloticase infusion and after the end of each pegloticase infusion prior to discharge from the site during the Pegloticase + MTX Period on Day 1, at the Weeks 2, 6, 10, 12, 14, 20 and 22; within 48 hours prior to each pegloticase infusion at Weeks 4, 8, 16, 18. Additional serum samples for sUA levels will be collected at non-infusion Visits at the End of Pegloticase Infusions Visit (if applicable) and the Week 24/End of study/Early Termination Visit and 3-

month Follow-up Visit. A subject with sUA level >6 mg/dL (based on the local or central laboratory) at 2 consecutive study visits, beginning with the Week 2 Visit, will be discontinued from pegloticase treatment and remain on study.If a subject's previous visit pre-infusion sUA was <6 m/dL – sUA result is not required for the following infusion visit (local pre-infusion sUA may be drawn at the same time as central pre-infusion sample). If a subject's previous visit pre-infusion sUA was >6 mg/dL – local sUA is required to be resulted (within 48 hours) to confirm stopping criteria was not met. See Section 9.6.2.1 and the Laboratory Manual for instructions for alternate scenarios. In the event of an AE suspected to be an IR, a serum sample will be collected at that time or at the subsequent visit for evaluation of pegloticase antibodies.

19. Serum samples for evaluation of anti-PEG antibodies and anti-uricase IgG antibodies will be collected prior to the infusion on Day 1 and at the Weeks 2, 6, 12, 20. An additional sample will be collected at each of the End of Study/Early Termination Visit and the 3-month Study Follow-up Visit. In the event of an AE suspected to be an IR, a serum sample will be collected in a SST tube at that time or at the subsequent visit for evaluation of anti-drug antibodies.
20. For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit; at the End-of-Study/Early Termination Visit.
21. For women of childbearing potential, a urine pregnancy test will be performed at all indicated visits and results must be confirmed by site personnel prior to any infusion starting. If the subject has not ovulated by the 30-day Follow-up email/phone call, the subject will be requested to return to the site for a urine pregnancy test.
22. Urine Albumin: Creatinine Ratio is derived data by the lab using results from urine.
23. 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. All subjects will be followed for a minimum of 3 months following Week 24/End-of-Study/Early Termination Visit.
24. Subjects who are non-vasectomized males will be asked 3 months after MTX discontinuation regarding partner pregnancy. This will occur at a regularly scheduled visit or by a separate phone/email visit.
25. Thirty (30) days after the last MTX dose, subjects will be contacted by telephone or email to review AEs and SAEs. Subjects who are females of childbearing potential will be asked to confirm that ovulation has occurred. If the subject has not ovulated, the subject will be requested to return to the site for a urine pregnancy test.

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
BID	Twice a day
BP	Blood Pressure
CFR	Code of Federal Regulations
CRP	C-Reactive Protein
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
HTI DAC	Horizon Therapeutics Ireland DAC
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	informed consent form
ICH	International Council for Harmonisation
IMM	Immunomodulator
IND	Investigational New Drug
IR	infusion reaction
IRB	Institutional Review Board
IV	intravenous(ly)
LLN	Lower limit of normal
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
mITT	modified intention-to-treat
MRI	Magnetic Resonance Imaging
MTX	methotrexate
NSAID	nonsteroidal anti-inflammatory drug
PK	pharmacokinetic(s)
RNA	ribonucleic acid

Abbreviation	Definition
SAE	serious adverse event
sUA	serum uric acid
TEAE	Treatment-emergent adverse event
TID	Three times a day
ULT	urate lowering treatment
ULN	Upper Limit of Normal
USP	United States Pharmacopeia

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

5 ETHICS

5.1 Institutional Review Board/Independent Ethics Committee

The Principal Investigator (Investigator), the Sponsor and/or designee authorized by the Sponsor will submit this protocol, any protocol modifications, the informed consent form (ICF) and all applicable 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 ICF process, the subjects will be informed in writing that representatives of the Sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

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

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

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

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Sponsor of this study is Horizon Therapeutics Ireland DAC (Horizon). Horizon personnel will serve as the Medical Monitor and the Sponsor's regulatory representative (see Section 17.1 for details). The Sponsor's regulatory representative, or designee will be responsible for timely reporting of serious adverse events (SAEs) to regulatory authorities, as required. The Sponsor

will be responsible for timely reporting of SAEs and any other new pertinent safety information to all Investigators, as required.

The study will be conducted at approximately 40 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.

7 INTRODUCTION

7.1 Background

7.1.1 Gout

Gout affects approximately 4% of the United States population, is the most common form of inflammatory arthritis in men and is associated with decreased quality of life [Saag and Choi, 2006; Singh and Strand, 2008; Zhu et al, 2011; Sattui et al, 2014]. The frequency of gout is increasing worldwide, with prevalence rates estimated to be as high as 7% in older men [Mikuls et al, 2005; Saag and Choi, 2006; Roddy and Doherty, 2010]. Up to 400,000 persons (up to 5% of the estimated 8 million persons with gout) in the United States experience chronic symptoms of gout, despite trials of urate-lowering therapy. Gout, which is sometimes referred to as chronic refractory gout, is characterized by ongoing symptoms of active disease and a failure to control/maintain serum uric acid (sUA) <6 mg/dL with conventional xanthine oxidase inhibitors (i.e., allopurinol and febuxostat) and uricosuric agents (i.e., probenecid) [AAC Briefing Document 2009; Brook et al, 2010; Wertheimer et al, 2013; Khanna et al, 2016]. These patients often have significant, disabling urate deposits in soft tissues and bone known as tophi.

7.1.2 Pegloticase

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

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

suggesting continuing benefit with extended pegloticase treatment beyond the initial 6 months of therapy, particularly in subjects who met responder criteria in the placebo-controlled trials.

In the phase 3 pivotal studies, deaths, AEs, SAEs, as well as the laboratory abnormalities were generally equally distributed across placebo and pegloticase treatment groups, with the clear exception of gout flares and 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 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.

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

7.1.2.1 Physiochemical Properties

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

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

7.1.2.2 Nonclinical Pharmacology

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

7.1.2.3 Non-clinical Pharmacokinetics

A series of pharmacokinetic (PK) studies was conducted in rats, rabbits, dogs and pigs to determine the circulation half-life and bioavailability as a function of the route of pegloticase administration. Plasma pegloticase levels were determined by assaying uricase bioactivity in

plasma. As part of the PK studies, antibody levels in plasma were determined 2 weeks after the last injection in the rabbit, dog and rat. Collectively, the results of the PK studies in these animals lend support to the expectation of high bioavailability and prolonged retention of pegloticase after administration in humans.

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

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

7.1.2.4 Toxicology

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

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

7.1.2.4.1 Clinical Pharmacokinetics

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

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

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

In patients undergoing hemodialysis (Study M0403), pegloticase serum concentrations were not clinically meaningfully affected by 2 hemodialysis sessions. Pre- and post-dialyzer samples, as

well as samples taken during dialysis, demonstrated that study drug was not removed by the dialysis process.

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

7.1.3 Risks of Pegloticase

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

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

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

It is required that all subjects receive prophylactic treatment to reduce the risk of acute gout flares, unless medically contraindicated or not tolerated, as noted in the pegloticase prescribing information. Subjects should begin a regimen of colchicine (0.6 mg/day) and/or NSAID and/or low-dose prednisone (≤10 mg/day) prophylaxis ≥1 week before the first dose of pegloticase and continuing flare prophylaxis throughout the pegloticase treatment period per American College of Rheumatology guidelines [Khanna D et al. 2012]. All subjects who experience a gout flare during the study will be prescribed anti-inflammatory treatment (e.g., NSAIDs, colchicine), as deemed clinically indicated by the study physician.

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

The risk of anaphylaxis and IRs is higher in patients whose sUA level increases to >6 mg/dL. Therefore, beginning with Week 2, 2 pre-dose blood samples (within 48 hours prior to dosing pegloticase) will be obtained to verify the sUA level is ≤6 mg/dL prior to infusion of pegloticase (see Section 9.6.2.1). A subject with sUA level >6 mg/dL at 2 consecutive study visits, beginning with the Week 2 Visit, will be classified as a non-responder and will be discontinued from pegloticase treatment, but continue on study as described in Section 9.4.3.

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

7.1.3.1 Safety

The principal safety risks associated with pegloticase include anaphylaxis, IRs and gout flares. Pegloticase has not been formally studied in patients with congestive heart failure, but some subjects in the clinical trials experienced exacerbation. Exercise caution when using pegloticase in patients who have congestive heart failure and monitor patients closely following infusion. The data support that monitoring of sUA and discontinuation of pegloticase therapy in patients who lose the ability to maintain uric acid <6 mg/dL can lead to the avoidance of the majority of IRs and unnecessary exposure to drug. The longer-term exposure evidenced by the open-label extension study supports the benefit-to-risk assessment of 8 mg of pegloticase IV every 2 weeks as an effective therapy in chronic gout patients, particularly those with tophi who are unresponsive to other therapies.

7.1.4 Risks of Methotrexate

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

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

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

Additionally, MTX can cause fetal death or teratogenic effects. Pregnancy should be avoided if either partner is receiving MTX, during and for a minimum of three months after MTX therapy for the non-vasectomized male. For females of child bearing potential, pregnancy should be avoided for at least one ovulatory cycle after MTX therapy. Refer to the current version of the FDA-approved MTX Full Prescribing Information for detailed information concerning the safety profile of MTX.

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

7.2 Rationale for this Study

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

Currently, pegloticase is FDA approved for intravenous administration over no less than 120 minutes [KRYSTEXXA Full Prescribing Information]. Pegloticase needs to be re-administered every two weeks to achieve optimal therapeutic outcomes and prevent elevations in sUA levels and reduce tophus burden [Baraf 2013]. Compliance with such a regimen can be burdensome and pose a barrier to treatment for some patients who may otherwise benefit from the infusion. Therefore, there is an unmet need for patients with uncontrolled gout to have access to a therapy that is effective with limited AEs, amenable to high patient compliance over several months. Administering pegloticase over a shorter duration time may address this unmet need.

One concern, however, is that a shorter infusion duration may lead to increased AEs. Pegloticase has been associated with IRs, including anaphylaxis. In a Phase 2 study in which pegloticase was administered at 30 minutes in the majority of subjects, 44% of subjects experienced an IR (no subjects experienced anaphylaxis). It is important to note that there was no methotrexate as part of the protocol and the majority of subjects did not receive any IR prophylaxis. In Phase 3 studies (which included IR prophylaxis for all subjects), with pegloticase administered over 120 minutes, IRs occurred in 26% of subjects receiving pegloticase compared to 5% of subjects receiving placebo and anaphylaxis was reported in 5% of subjects receiving pegloticase and 0% of subjects receiving placebo (pegloticase (KRYSTEXXA) Investigator's Brochure). The nature and the severity of the IRs in the Phase 2 and Phase 3 studies were relatively similar. These AEs are thought to be related to the development of anti-drug antibodies and can be reduced by avoiding infusions in patients who initially respond and then have a rebound of their serum uric acid above 6 mg/mL. These anti-drug antibodies are also associated with loss of efficacy as reflected in this increase in sUA levels [Schellekens 2005; Sundy et al, 2011].

Reducing anti-drug antibodies via pre-treatment with and concomitant administration of an immune-modifying drug, methotrexate (MTX), has been shown to be useful in other infused products, such as infliximab, in the setting of rheumatoid arthritis treatment. Based on results from MIRROR RCT (NCT03994731), pretreatment and coadministration of pegloticase with methotrexate 15 mg orally once weekly was shown to significantly reduce failure rates and the incidence of infusion reactions in patients with chronic gout as compared to pegloticase alone [Botson et al, 2022].

To address the possibility of increased AEs with a shorter infusion duration, this study will incorporate an IR prophylaxis regimen as well as pre-treatment and concomitant use of MTX with pegloticase [Hershfield et al, 2014].

Individual subject sUA Discontinuation Criteria will also be in place to minimize the potential for AEs in subjects who are non-responders to treatment. Since the risk of anaphylaxis and IRs is higher in patients who have lost therapeutic response, this study will also discontinue treatment if sUA levels increase to above 6 mg/dL at 2 consecutive study visits to minimize the potential for such AEs.

7.3 Rationale for Dose Selection

The current approved dose of pegloticase for intravenous infusions, 8 mg every 2 weeks, will be tested in this study. Refer to the current version of the FDA-approved KRYSTEXXA Full Prescribing Information.

The study will be initiated enrolling subjects assigned to 60-minute infusion durations. Based on tolerability, this infusion duration may be progressively shortened to 45-minute and 30-minute infusions. A previous trial (n=41) was conducted using 30 minute and 60 minute infusions. The adverse event profile was similar in nature and severity to that which is seen with the FDA-approved 120 minute infusions [Sundy et al, 2008]. The consistent adverse event profile supports initiating this trial with subjects receiving infusions at 60 minute durations and progressively moving to shorter durations of 45 minutes and 30 minutes.

8 STUDY OBJECTIVES

The overall objective of this study is to assess the tolerability and efficacy of pegloticase administered with a shorter infusion duration in subjects with uncontrolled gout receiving methotrexate.

Primary Objective

The primary objective is to assess the tolerability of pegloticase infusions administered with methotrexate (MTX) from Day 1 through Week 24 in the cohort chosen to be most desirable duration for infusion, as measured by the incidence of IRs (including anaphylaxis) related to pegloticase.

Secondary Objectives

The secondary objectives will be assessed for the cohort chosen to be the most desirable duration for infusion and include:

- Estimate the response rate at Month 6 (Weeks 20, 22 and 24), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 6.
- Assess the proportion of subjects receiving pegloticase with MTX who experienced any of the following events: Infusion Reaction (IR) leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria.

- Assess the time to any of the following events: IR leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria (two consecutive pre-infusion sUAs >6 mg/dL).

Exploratory Objectives

- Assess the pharmacokinetics of pegloticase.
- Assess the profile of anti-uricase antibodies and anti-poly (ethylene glycol) antibodies.

Safety Objectives

- Assess the incidence of adverse events of special interest (AESI), including IRs, anaphylaxis, gout flares, cardiovascular events and the AE/SAE profile overall.
- Assess the proportion of subjects who experienced IR leading to slowing down of the infusion rate or discontinuation of treatment.
- Assess the time to first IR leading to slowing down of the infusion rate or discontinuation of treatment.
- Assess the time to first IR.
- Assess the proportion of subjects who were able to complete all infusions over the assigned treatment duration length or a lesser time, without clinically requiring an increased infusion time.
- Assess the proportion of infusions completed over the assigned duration length or a lesser time, without clinically requiring an increased infusion time.
- Laboratory tests and 12-lead electrocardiogram (ECG).
- Vital signs and physical examinations.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a Phase 4, multicenter, open-label, infusion duration, study of pegloticase administered over < 120 minutes in combination with MTX to evaluate the safety, tolerability and efficacy in treating adult subjects with uncontrolled gout.

Approximately 10 subjects in each cohort are planned to be enrolled initially. If deemed safe, an additional 100 subjects to be enrolled in the selected cohort in order to have approximately 110 subjects exposed. Treatment duration with pegloticase will be approximately 24 weeks.

The study design will include: 1) a Screening Period, lasting up to 35 days; 2) a 4-week MTX Run-in Period; 3) a 24-week Pegloticase + MTX Period which includes an End-of study Week 24/Early Termination Visit; 4) a safety Follow-up Phone/Email 30 days after the last pegloticase infusion and 5); a 3-month Post-Treatment Follow-up.

Guidance on Blood Glucose Monitoring:
HbA1c testing must be performed at Screening for all subjects (locally or centrally):
If HbA1c >6.5% and/or if subject has known diagnosis of diabetes mellitus, *additional measures* are recommended:

- Investigator asked to closely monitor glucose levels and adjust any diabetic medications as necessary
- Subject should consult their primary care physician and/or Endocrinologist managing their diabetes

The pre-infusion IV steroid dose may be reduced (e.g., methylprednisolone 75 mg IV) after consulting with the Horizon Medical Monitor.

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

Subjects will also take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) continuing until prior to the End of Pegloticase Infusion Visit (if applicable) or the Week 24/End of Study/Early Termination Visit. Subjects must be able to tolerate MTX at a dose of 15 mg during the 4-week MTX Run-in Period (prior to Day 1) to be eligible to participate in the Pegloticase + MTX Period. Subjects who are unable to tolerate MTX at a dose of 15 mg during the MTX Run-in Period will be considered screen failures and not proceed to pegloticase dosing.

Female subjects who take at least one dose of MTX and who are of childbearing potential, will receive a safety Follow-up phone call/e-mail approximately 30 days after the last dose of MTX to verify at least one ovulatory cycle has occurred after the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. For male subjects who take at least one dose of MTX and who are non-vasectomized an inquiry will be conducted at the Post-Treatment 3-month Follow-up visit (or 3 months after the subject's last dose of MTX) after MTX discontinuation regarding partner pregnancy.

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

It is required that before a subject begins the Pegloticase + MTX Period, he or she has been taking at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or

NSAIDs and/or low-dose prednisone ≤10 mg/day) for ≥1 week before the first dose of pegloticase and continuing flare prophylaxis per American College of Rheumatology guidelines [Khanna D et al. 2012].

For IR prophylaxis, fexofenadine (180 mg orally) will be taken the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, immediately prior to each infusion.

During the Pegloticase + MTX Period, all subjects will receive pegloticase 8 mg every 2 weeks administered IV for a total of 12 infusions from Day 1 through Week 22, inclusive for a total of 12 infusions; pegloticase will be administered after all pre-dose study visit assessments have been completed at each visit. The date and start and stop time of infusion will be recorded. sUA Discontinuation Criteria will be applied: subjects with sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue treatment but continue on study as described in Section 9.4.3.

Up to three pegloticase infusion durations may be assessed for the Pegloticase + MTX Period:

- 60-minute infusion
- 45-minute infusion
- 30-minute infusion

Initially, cohorts of approximately 10 subjects will be enrolled sequentially at progressively shorter infusion durations initially, beginning with the 60-minute infusion duration, progressing down to the 45-minute infusion duration and then to the 30-minute infusion duration. If deemed safe, enrollment will continue in the chosen infusion duration cohort until approximately 110 subjects are enrolled (e.g. targeted 110 subjects in the 30-minute infusion cohort, unless 30-minute infusion is not tolerated, then approximately 110 subjects may be enrolled in the 45-minute or 60-minute infusion cohort). The most desirable infusion duration is the shortest duration which is shown to be safe and well tolerated.

After the first 3 subjects at each infusion duration complete at least 4 weeks of Pegloticase + MTX period (3 infusion visits), a holistic safety assessment will be performed by the internal Safety Review Committee on available subjects' data. Study enrollment will not be paused. If a subject discontinues treatment or study prior to the third infusion visit, their available data is still included in the safety assessment. If the safety assessment indicates that the infusion duration is well tolerated (based on pre-determined criteria, see Section 9.2), then additional safety assessments will continue to be performed based on available subjects' data after 6 subjects and 10 subjects complete at least 4 weeks of the Pegloticase + MTX period (3 infusion visits).

If the Safety Review Committee confirms that the percentage of subjects meeting infusion speed-limiting criteria is less than the threshold specified in Section 9.2, then enrollment of subjects at the next progressively shorter infusion duration cohort (15 minutes shorter duration) will begin. Further, if the Safety Review Committee confirms that the percentage of subjects meeting infusion speed-limiting criteria are less than the thresholds specified in Section 9.2,then

additional subjects will be enrolled (for a total of approximately 110 subjects in the given cohort).

If any of the safety assessments indicate that a specific infusion duration is not tolerated based on pre-determined criteria, then the study may enroll additional subjects at any infusion durations. In the event that the initial 60-minute infusion duration is not tolerated based on pre-determined criteria, then the study may be revised or terminated (after internal review and assessment).

If >10 subjects are enrolled at any infusion duration, additional safety assessments will be performed when 15 subjects and 20 subjects complete at least 4 weeks of the Pegloticase + MTX period (3 infusion visits).

Once all subjects have at least 4 weeks of Pegloticase + MTX period (3 infusion visits), additional safety assessments will be done as needed (refer to the Safety Review Committee charter). If a subject discontinues treatment or study prior to either of these time-points, their available data is still included in the safety assessment.

The Safety Review Committee can modify the number of subjects at the chosen infusion duration, if they determine that more safety data is needed.

Investigators will be permitted to adjust the duration of the infusion at a particular infusion visit regardless of initial treatment duration assignment, if needed. The decision to modify the infusion duration at a visit, will be allowed based on the investigator's discretion, after a discussion with the Medical Monitor.

Subjects may return to the original infusion duration for subsequent infusions at investigator's discretion.

Pegloticase will be administered after all pre-dose study visit assessments have been completed at each visit. The date and time of infusion start and stop will be recorded.

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

After Day 1, if a subject becomes unable to tolerate 15 mg of MTX, the MTX dose may be reduced and/or discontinued and the subject may remain in the study (see Section 9.5.7.3.2.2).

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

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

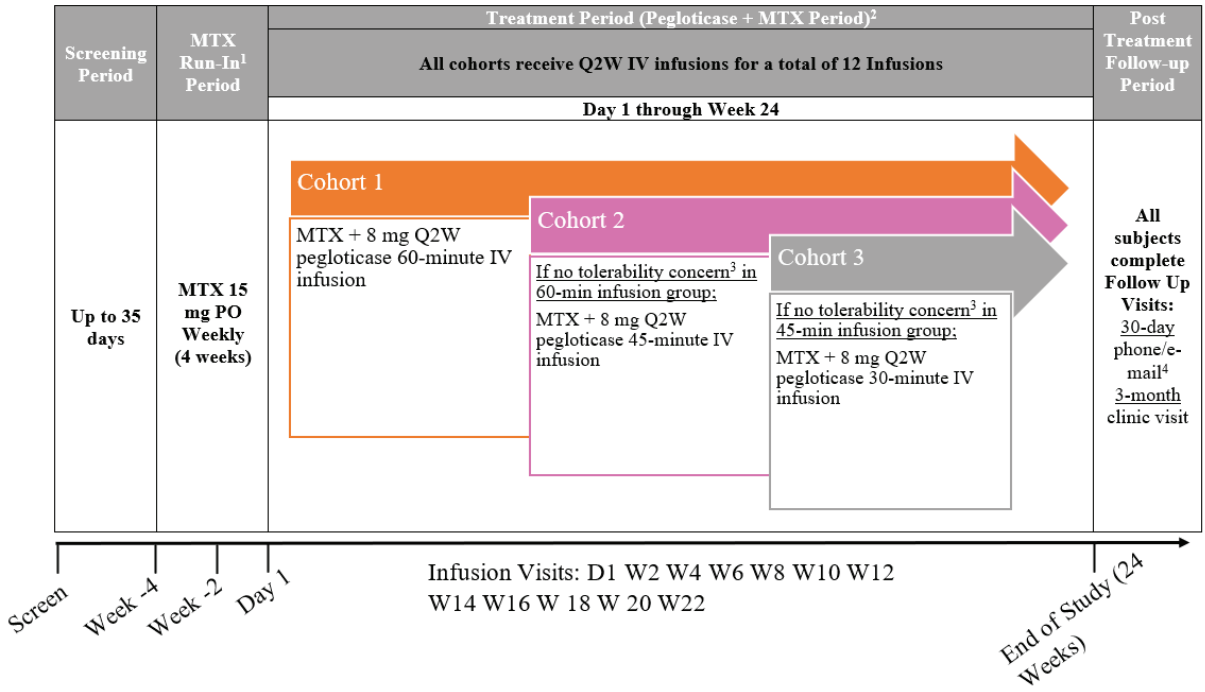
The total blood volume to be collected from each subject during this study is approximately 450 mL.

An External Adjudication Committee will be established for this study to adjudicate the AESIs. The External Adjudication Committee will be comprised of external experts with experience in immunology, allergic reactions, rheumatology and/or cardiovascular diseases. Details outlining the responsibilities of the Adjudication Committee will be included in the Adjudication Committee charter. AESIs defined in the protocol (See Section 9.6.1.2.1.5) include IRs, anaphylaxis and cardiovascular events. The AESI of gout flare will not be adjudicated.

Aggregate safety data will be reviewed by the internal Safety Review Team (SRT) and Safety Review Committee (SRC). Subject safety and tolerability of the pegloticase regimen will be discussed to establish a recommendation as whether to continue the current treatment regimen or to modify the assigned treatment regimen.

The SRC will be comprised of members of the Horizon Clinical Development and Patient Safety and Pharmacovigilance Teams. Meetings will occur at pre-determined timepoints or ad-hoc dependent on any potential safety signals reported (e.g. anaphylaxis or any SAE related to pegloticase infusion). If any anaphylaxis event or SAE related to pegloticase infusion occurs with any subject, real-time with expedited review of patient profiles and/or relevant data available in the electronic data capture will occur. Changes may include, but are not limited to, increasing the pegloticase infusion duration or modifying the methotrexate dosage. An overview of the study design is presented in the schematic below and details of study activities are provided in Section 9.1.

Figure 9.1 Schematic of Study Design



IV = intravenous; MTX = methotrexate; PO = oral; Q2W = every 2 weeks; W = week
Note: Study visits must be completed within ±3 days of the target visit date.

1. Prior to the Treatment Period, subjects will begin taking at least one of the per protocol standard gout flare prophylaxis regimen (colchicine 0.6 mg/day and/or NSAID and/or low dose prednisone <10 mg/day) for ≥1 week before the first dose of pegloticase and continuing flare prophylaxis throughout the pegloticase treatment period per American College of Rheumatology guidelines. For IR prophylaxis, fexofenadine (180 mg orally) will be taken the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) over an infusion duration between 10 and 30 minutes, will be administered immediately prior to each infusion.
2. Stopping rules will be implemented: Subjects with 2 sUA levels > 6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue from pegloticase therapy and complete the End of Pegloticase Infusions Visit and remain on study.
3. The determination on whether to enroll the next cohort of subjects to a different infusion duration level will be based on whether the previous cohort meets the Infusion Speed-Limiting Criteria as well as the Safety Review Committee decision.
4. All subjects will receive a safety follow-up phone call/e-mail approximately 30 days after the last dose of pegloticase to assess if any SAEs have occurred. If the subject discontinues treatment but continues in the study, then this follow-up visit may be replaced by a scheduled study visit.

9.2 Infusion Speed-Limiting Criteria

Infusion speed-limiting criteria will be met if a subject experiences any severe (Grade ≥3) IRs or any other severe AEs within 24 hours of receiving pegloticase infusion and attributed to the infusion and not any other underlying disease process. The signs and symptoms of the severe IRs are usually prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief

interruption of infusion) or recurrent following initial improvement. Possible associated signs and symptoms of IRs may include but not limited to:

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

If ≤ one-eighth of subjects meet infusion speed-limiting criteria at the same infusion duration after 3 subjects and after 6 subjects, then enrollment may continue at the same infusion duration. If ≤ one-third of subjects meet infusion speed-limiting criteria at the same infusion duration after 10 subjects, then enrollment may continue at the next progressively shorter infusion duration.

If > one-eighth of subjects meet infusion speed-limiting criteria, then enrollment at that infusion duration may be suspended.

Safety Review Committee must confirm that infusion speed-limiting criteria were met, prior to additional patients being enrolled at the previous infusion duration. In the event that > one-eighth of subjects meet infusion-speed limiting criteria at the initial 60-minute infusion duration, then the study may be revised or terminated (after internal review and assessment).

If an anaphylaxis event occurs in any subject, further dosing with pegloticase for that subject will be terminated.

If any anaphylaxis event or SAE related to pegloticase infusion occurs with any subject, all pertinent data will be provided for expedited review to the Adjudication Committee (for the purpose of adjudicating AESIs) and the SRT/SRC.

If any anaphylaxis event or SAE related to pegloticase infusion occurs with any subject, real-time with expedited review of patient profiles and/or relevant data available in the electronic data capture will occur.

9.3 sUA Discontinuation Criteria

Individual Subject sUA Discontinuation Criteria: Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue treatment and remain in the study for Follow-Up visits only, including the 30-day Follow-up Email/Phone call, Week 24/End of Study/Early Termination and 3 Month Post-Treatment Follow-up Visits.

Note: The sUA Discontinuation Criteria only pertain to individual subjects and are not sUA Discontinuation Criteria for a group or specific infusion duration.

9.4 Selection of Study Population

Subjects diagnosed with gout eligible for this study will have sUA ≥6 mg/dL and inability to maintain sUA <6 mg/dL on other urate-lowering therapy or intolerable side effects associated with current urate-lowering therapy, or with a contraindication to xanthine oxidase inhibitor therapy.

9.4.1 Inclusion Criteria

Eligible subjects must meet all of the following criteria:

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

injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or vasectomized partner.

7. Men who are not vasectomized must agree to use appropriate contraception so as to not impregnate a female partner of reproductive potential during the study, beginning with the initiation of MTX at Week -4 and continuing through 3-Month Post-Treatment Follow-up.
8. Able to tolerate MTX 15 mg for 4 weeks during the MTX Run-in Period prior to the first dose of pegloticase.

9.4.2 Exclusion Criteria

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

1. Weight >160 kg (352 pounds) at Screening.
2. Any serious acute bacterial infection, unless treated and completely resolved with antibiotics at least 2 weeks prior to Week -4 Visit.
3. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis.
4. Current or chronic treatment with systemic immunosuppressive agents such as MTX, azathioprine, or mycophenolate mofetil; prednisone ≥10 mg/day or equivalent dose of other corticosteroid on a chronic basis (defined as 3 months or longer) would also meet exclusion criteria.
5. Known history of any solid organ transplant surgery requiring maintenance Immunosuppressive therapy unless treated and no chronic or active infection confirmed by HBV serology.
6. Known history of hepatitis B virus surface antigen positivity or hepatitis B DNA positivity, unless treated and viral load is negative and no chronic or active infection confirmed by HBV serology.
7. Known history of hepatitis C virus RNA positivity unless treated and viral load is negative.
8. Known history of Human Immunodeficiency Virus (HIV) positivity
9. Glucose-6-phosphate dehydrogenase (G6PD) deficiency (tested at Screening Visit).
10. Severe chronic renal impairment (estimated glomerular filtration rate <40 mL/min/1.73 m^2) at the Screening Visit based on the 4 variable-Modification of Diet in Renal Disease [MDRD] formula or currently on dialysis.
11. Non-compensated congestive heart failure or hospitalization for congestive heart failure or treatment for acute coronary syndrome (myocardial infarction or unstable angina) within 3 months of the Screening Visit, or current uncontrolled arrhythmia, or current uncontrolled BP (>160/100 mmHg) prior to Week -4.
12. Pregnant, planning to become pregnant, breastfeeding, planning to impregnate female partner, or not on an effective form of birth control, as determined by the Investigator.

13. Prior treatment with pegloticase (KRYSTEXXA), another recombinant uricase (rasburicase), or concomitant therapy with a polyethylene glycol-conjugated drug.
14. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product.
15. Contraindication to methotrexate (MTX) treatment or MTX treatment considered inappropriate.
16. Known intolerance to MTX.
17. Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to MTX administration at Week - 4, or plans to take an investigational drug during the study.
18. Liver transaminase levels (AST or ALT) > upper limit of normal (ULN) or albumin < the lower limit of normal (LLN) at the Screening Visit.
19. Chronic Liver Disease.
20. White blood cell count < 4,000/ul, hematocrit < 32 percent, or platelet count <75,000/ul.
21. Currently receiving systemic or radiologic treatment for ongoing cancer.
22. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix.
23. Uncontrolled hyperglycemia with a plasma glucose value >240 mg/dL at Screening that is not subsequently controlled by the end of the Screening.
24. Diagnosis of osteomyelitis.
25. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
26. 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.
27. Alcohol use in excess of 3 alcoholic beverages per week.
28. A known intolerance to all protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤10 mg/day).
29. Currently receiving urate-lowering therapies and unable to discontinue treatment at least 7 days prior to MTX dosing at Week -4 and remain off of urate lowering therapy when receiving pegloticase infusions during the study.
30. Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest X-ray may be performed during Screening

9.4.3 Removal of Subjects from Therapy or Study

Every effort should be made to retain a subject in the study to monitor their safety for at least 3-months of follow-up. Subjects who are removed from pegloticase therapy should remain on study for Follow-Up visits only, including the 30-day Follow-up Email/Phone call, Week 24/End of Study/Early Termination and 3 Month Post-Treatment Follow-up Visits barring withdrawal of consent for study participation. However, subjects may withdraw consent or discontinue participation from the study at any time, without prejudice to further treatment. In addition, the Investigator may discontinue a subject from treatment at any time. The primary reason for discontinuation from the study and/or study drug should be recorded on the eCRF.

9.4.3.1 Removal of Subjects from Pegloticase Therapy

For subjects who do not complete 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 of Consent. Subject refusal of additional therapy (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
- Death

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

- Methotrexate, along with folic acid, will be discontinued at the time of cessation of pegloticase infusions prior to Week 24.
- All subjects will complete the End of Pegloticase Infusions Visit and should be encouraged to remain on study and attend all Follow-Up visits, including the 30-day Follow-up Email/Phone call, Week 24/End of Study/Early Termination and 3 Month Post-Treatment Follow-up Visits barring withdrawal of consent from study participation.
- Activities related to pre/post infusion monitoring or medication dispensation will not be completed once a subject has stopped pegloticase infusions. These activities include:
    - MTX compliance/reconciliation

- IR prophylaxis
- IR prophylaxis compliance
- Folic acid compliance
- Pegloticase infusion
- Pegloticase PK sampling
- Pre-infusion MTX Polyglutamate sampling
- MTX drug/dispensation related items

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.

9.4.3.2 Removal of Subjects From Study

In addition to completion of therapy, the Follow-Up visits, the Week 24 visit and the reason for discontinuation from the study should be recorded on the eCRF using one of the following categories:

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

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. At least two phone calls and a registered letter should be documented before considering subject lost to follow-up. When a subject withdraws before completing the study, attempts of follow-up information should be documented in the source documents to include reasons of withdrawal.

9.4.4 Replacement Policy

9.4.4.1 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.

9.4.4.2 Centers

A center may be closed and/or replaced for several reasons. Prior to a site being recommended for closure, the site PI, Medical Monitor, Study Manager and possibly the Site Monitor will discuss the decision for closure.

9.4.4.3 Screen Failures

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

Screen failure subjects may be allowed to rescreen for the study if both the Investigator and Sponsor are in agreement regarding rescreening and if the Investigator determines that the subject can satisfy all of the eligibility criteria.

9.5 Treatments

9.5.1 Treatment Assignment

This is an open-label, non-randomized study therefore the study site personnel, sponsor and patient will all know the treatment.

The treatment assignment is coordinated centrally by the Sponsor.

After the investigator/study site identifies a potential patient, the investigator/study site should notify sponsor of potential patient by sending a Screening Notification email to the Study Manager and Medical Monitor. Formal screening procedures should not begin until a slot has been confirmed for any potential patient. The Sponsor will confirm that the patient is held a spot for potential treatment.

At any time, the study can end prior to the potential patient getting dosed.

9.5.2 Treatments Administered

Methotrexate

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

Subjects will be instructed to take MTX weekly on the same day each week (if dosing more frequently than once in a day (i.e. BID, TID), the total weekly MTX dose should be taken within

24 hours, preferably the same calendar day) and record the date and time of each dose in the dosing calendar.

During the MTX Run-in Period, if a dose is missed, it should be taken as soon as it is remembered. If it is within 48 hours of the next scheduled dose, the subject will be instructed to skip the missed dose and resume at the next regularly scheduled time; thus, subjects will be instructed not to double a dose to make up for a missed dose if within 48 hours of the next dose. Investigators may choose to have subjects take the weekly dose divided over the day (i.e. BID, TID).

During the Pegloticase + MTX Period, MTX should be taken 1 to 3 days prior to the pegloticase infusion and one additional weekly dose after the last infusion (at Week 22) for subjects who have not stopped pegloticase due to study sUA Discontinuation Criteria. If a subject is not able to take the MTX 1 to 3 days prior to the pegloticase infusion, MTX must be taken ≥60 minutes prior to the pegloticase infusion.

During the Pegloticase + MTX Period, if a subject becomes unable to tolerate the MTX the dosage may be decreased.
Subjects will also take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the Week 24 Visit.

Pegloticase

All subjects who meet the inclusion/exclusion criteria and tolerate oral MTX 15 mg weekly during the MTX Run-in Period will receive pegloticase at a dose of 8 mg administered IV every 2 weeks for a total of 12 infusions from Day 1 through Week 22 inclusive (Pegloticase + MTX Period). The date and start and stop time of infusion will be recorded. Subjects will not be fasting on the day of infusion and will be encouraged to have a snack or normal meal before or after the infusion.

All subjects will receive standardized prophylactic treatment to reduce the risk of acute gout flares, beginning ≥1 week before the first dose of pegloticase and continuing flare prophylaxis throughout the pegloticase treatment period per American College of Rheumatology guidelines [Khanna D et al. 2012].

Standardized IR prophylaxis consisting of pre-treatment with an antihistamine, acetaminophen and a corticosteroid will accompany each infusion.

9.5.2.1 Folic Acid

Subjects will take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the Week 24/End of Study/Early Termination Visit.

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

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

9.5.2.2 Gout Flare Prophylaxis

It is required that before a subject begins the Pegloticase + MTX Period, he or she has been taking at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or NSAIDs and/or lowdose prednisone ≤10 mg/day) for ≥1 week before the first dose of pegloticase and continuing flare prophylaxis throughout the pegloticase treatment period per American College of Rheumatology guidelines [Khanna D et al. 2012].

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.

9.5.2.3 Infusion Reaction Prophylaxis

Since IRs can occur with pegloticase, all subjects will receive IR prophylaxis prior to each infusion, consisting of an antihistamine, acetaminophen and a corticosteroid. To standardize this regimen, subjects will receive fexofenadine (180 mg orally) the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, immediately prior to each infusion. Substitution of the corticosteroid is not allowed. The name, dose, route, date and time of administration of each prophylactic medication will be recorded in the medical record and in the eCRF. The Solumedrol used for IR prophylaxis will be supplied by the site. Other IR medications administered prior to each infusion may also be supplied by the site.

NOTE: If subject's HbA1c is >6.5% at Screening and/or if subject has known diagnosis of diabetes mellitus, the pre-infusion IV steroid dose may be reduced (e.g., methylprednisolone 75 mg IV) after consulting with the Horizon Medical Monitor.

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.

9.5.3 Identity of Investigational Products

9.5.3.1 Pegloticase

<u>8 mg/mL Uricase:</u>

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

0.16 mg/ml Uricase:

Pegloticase is a clear, colorless, sterile solution in phosphate-buffered saline provided for ready-to-use for IV infusion. 50 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.

9.5.3.2 Methotrexate

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

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

9.5.4 Labeling

Pegloticase (KRYSTEXXA) is commercially available as 8 mg/mL uricase in the United States and will be supplied by PCI Pharma Services packaged in sterile, single-use 2-mL glass vials with 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.

The alternative ready-to-use presentation of pegloticase (0.16 mg/ml uricase) will be supplied by PCI Pharma Services packaged sterile, single-use 50-mL glass vials with a Fluorotec-coated rubber injection stopper which delivers 8 mg uricase in a 50 mL solution. An ancillary label will be fixed to the vial and carton that identifies the study, allows subject information to be entered and contains the investigational use caution statement according to the FDA Title 21 CFR Part 312 requirements. Each vial label will have a unique number.

MTX will be provided to sites by PCI Pharma Services as tablets in bottles. An ancillary label will be fixed to the bottle that identifies the study, allows subject information to be entered and contains the investigational use caution statement according to the FDA Title 21 CFR Part 312 requirements. Each bottle label will have a unique number. Bottles will be provided to study subjects after the Week -4 Visit for weekly dosing after visit procedures and inclusion/exclusion criteria are confirmed.

9.5.5 Storage

Before preparation for use, pegloticase will be stored in the carton, maintained under refrigeration between 2ºC and 8ºC (36ºF and 46ºF), protected from light and will not be shaken or frozen.

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

MTX will be stored between 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature] and protected from light.

9.5.6 Drug Accountability

Clinical supplies will be dispensed only in accordance with the protocol. Accurate records of the clinical supplies received, the amount dispensed for each subject and the amount remaining at the conclusion of the study will be maintained. Each study site will also maintain subject drug logs/electronic logs to account for MTX dispensed and subject compliance will be monitored by the site at each visit (see Section 9.5.11).

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

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

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

9.5.7 Study Drug Administration and Timing of Dose for each Subject

9.5.7.1 Description of Clinical Supplies

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

9.5.7.2 Determination of Dose Volume

Pegloticase will be administered as an admixture of 8 mg in 50 mL of 0.45% or 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) for IV infusion. Alternatively, pegloticase is administered as a ready-to-use solution with 8 mg uricase formulated in 50 mL phosphate-buffered saline that is suitable 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. Modifications to the infusions at subsequent visits following an IR can be discussed with Medical Monitor.

9.5.7.3 Details Concerning Timing and Dose Administration

9.5.7.3.1 Preparation and Administration

9.5.7.3.1.1 Preparation

8 mg/mL Uricase:

Vials of pegloticase will be visually inspected for particulate matter and discoloration before administration, whenever solution and container permit. Vials should 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 50 mL bag of 0.45% or 0.9% Sodium Chloride Injection, USP for IV infusion and will not be mixed or diluted with other drugs. The infusion bag containing the dilute pegloticase solution will be inverted a number of times to ensure thorough mixing but will not be shaken. In accordance with good pharmacy practice, gloves will be worn during preparation of the dose.

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

0.16 mg/ml Uricase:

Vials of pegloticase of the alternative ready-to-use presentation (50 mL) will be visually inspected for particulate matter and discoloration before administration, whenever solution and container permit. Vials should not be used if either is present.

Before administration, allow the solution of pegloticase to reach room temperature. Pegloticase must never be subjected to artificial heating.

9.5.7.3.1.2 Dose and Administration

Methotrexate

All subjects will take oral MTX at a dose of 15 mg weekly.

Folic Acid

All subjects will take folic acid 1 mg orally daily. Folic acid will be supplied by a local pharmacy.

Pegloticase

All 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 Week 24, inclusive (Pegloticase + MTX Period). Subjects will not be fasting on the day of infusion and will be encouraged to have a snack or normal meal

before or after the infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion (see Section 9.6.2.1).

Standardized IR prophylaxis consisting of pre-treatment with antihistamines, acetaminophen and corticosteroids will accompany each infusion (see Section 9.5.2.3).

Pegloticase will be administered either as a ready-to-use 0.16 mg/mL IV solution (50 mL) or an admixture of 8 mg in 50 mL of 0.45% or 0.9% Sodium Chloride Injection, USP for IV infusion by gravity feed or infusion pump. After approximately 30 subjects in 30 min cohort receive admixture of 8 mg in 50 mL of 0.45% or 0.9% Sodium Chloride Injection, USP for IV infusion, newly enrolled subjects will be assigned to ready-to-use 0.16mg/mL IV solution (50 mL). Pegloticase will not be administered as an IV push or bolus.

In a patient with IV site, using tubing with no in-line filter, the pegloticase preparation will be infused over approximately 30 to 60 ±5 minutes, depending on cohort assignment, while the subject is under close observation for any signs of distress. If an in-line filter is used, it should be 0.2 µm or larger. At the end of the infusion, the IV line will be flushed with 10 mL of normal saline to ensure the full dose is administered. The date and time of infusion start and stop (inclusive of the IV flush) will be recorded.

9.5.7.3.2 Dose Modifications, Interruptions and Delays

9.5.7.3.2.1 Pegloticase Modifications

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

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

9.5.7.3.2.2 MTX Dose Algorithm and Intolerance Criteria

During the MTX Run-in a subject will be considered a screen failure if any of the following new laboratory findings or symptoms reflecting MTX intolerance occur:

1. Abnormal Hematology findings:
    a. WBC < 3.5 x 10^9/L
    b. Platelets < 75 x 10^9/L
    c. Hematocrit < 32%
2. Abnormal hepatic function findings:
    a. AST/ALT >1.5 x upper limit of reference range and

   b. Albumin < lower limit (LLN) of reference range
3. Abnormal renal function: eGFR <30ml/min/1.73 m^2 (as estimated with the MDRD equation).
4. New clinically important signs and symptoms, such as the following:
   a. Rash or oral ulceration
   b. Persistent nausea, vomiting and diarrhea
   c. New or increasing dyspnea or dry cough, or unexplained cough with fever
   d. Severe sore throat, abnormal bruising
   e. Severe headaches, fatigue and problems concentrating

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

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

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

* New clinically important symptoms or important medical events:

   a. Rash or oral ulceration
   b. Persistent nausea, vomiting and diarrhea
   c. New or increasing dyspnea or dry cough, or unexplained cough with fever
   d. Severe sore throat, abnormal bruising
   e. Severe headaches, fatigue and problems concentrating

f. Any other important medical events that might increase methotrexate toxicity or pre-dispose to new or worsening infection (e.g. undergoing surgery, hospitalization, being treated with antibiotics, having a clinical infection, developing new clinically significant pericardial / pleural effusion or ascites)

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

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

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

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

1. When liver enzymes return to values ≤1.5 × ULN, increase MTX or dose by 2.5 mg and reassess in 2 weeks.
2. If liver enzymes remain ≤1.5 × ULN, increase MTX or dose by 2.5 mg and reassess in 2 weeks.

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

9.5.7.3.2.3 Gout Flare Treatment

An increase in gout flares is frequently observed upon initiation of urate lowering treatment (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 9.6.1.10. 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.

9.5.7.3.2.4 Infusion Reaction Treatment

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

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

- A physical examination will be performed to capture medically relevant details, including, but not limited to, a thorough dermatologic examination for detection of erythema, urticaria (hives), or peri-oral or lingual edema; a chest examination for breath sounds, stridor or wheezing; and a cardiac examination with attention to irregular heartbeat.
- Vital signs (sitting or supine BP, heart rate, respiratory rate and body temperature) will be captured at least every 30 minutes until the resolution or stabilization of the AE.
- A 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 9.6.1.2.1.5), 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 9.6.1.2.1.5) or does not meet serious criteria, the Investigator may elect to initiate the next infusion at a slower rate. Additionally, the Investigator may choose to prescribe prednisone (e.g. 20 mg) to be taken in the morning of the next infusion. All changes to infusion rate or dilution and drugs given for prophylaxis or treatment, are to be recorded in the medical record and in the eCRF.

9.5.8 Method of Assigning Subjects to Treatment Groups

This study is an open-label, single-arm design in which all subjects will receive the same study drugs (i.e., MTX and pegloticase). Study will be initiated enrolling patients assigned to 60 minute infusion durations. Infusion duration assignment may be progressively shortened to 45 minute or 30 minute infusion durations based on tolerability of previous subjects and the infusion duration cohort may be modified based on the safety and tolerability assessments.

This is an open-label, non-randomized study therefore the study site personnel, sponsor and patient will all know the treatment.

The treatment assignment is coordinated centrally by the Sponsor.

At any time, the study can end prior to the potential patient getting dosed.

9.5.9 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 and up to the Screening Visit (as well as history of COVID-19 vaccinations).

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, COVID-19 vaccines), over the counter medications, herbal medications, vitamins and food supplements.

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

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

9.5.10 Restricted Medications

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

- Oral urate-lowering therapies including allopurinol, febuxostat, probenecid, lesinurad, or other ULT for gout; 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
- Any other investigational agent
- Methotrexate (other than study investigational product), azathioprine, mycophenolate mofetil, or other systemic immunosuppressants aside from glucocorticoids for gout flare prophylaxis (< 10 mg prednisone or equivalent per day) or intermittent gout flare treatment
- If a subject is treated with antibiotics, refer to Section 9.5.7.3.2.2.
- Systemic immunosuppressive agents

9.5.11 Treatment Compliance

A dosing calendar will be provided to subjects at the Week -4 Visit for recording each dose of MTX on each calendar day of MTX administration (Additional calendar pages may be provided at future visits as required). The dosing calendar and bottle of MTX should be brought to each study visit for assessment of compliance with MTX. Adherence to the MTX regimen will also be recorded by the study coordinator at study visits in the eCRF by recording the date of each MTX dose (mg), frequency and time of each dose per calendar day. Subjects who have taken at least 80% of the protocol specified amount of MTX will be considered compliant. Noncompliant subjects will be re-educated on compliance.

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

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

9.5.12 Contraception Requirements

Women of childbearing potential (including those with an onset of menopause <2 years prior to screening, non-therapy-induced amenorrhea for <12 months prior to screening, or not surgically sterile [absence of ovaries and/or uterus]) must agree to use 2 reliable forms of contraception during the study, one of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started ≥1 full cycle prior to Week -4 (start of MTX dosing) and continue for 30 days after the last dose of pegloticase or at least one ovulatory cycle after the last dose of MTX (whichever is the longest duration after the last dose of pegloticase or MTX).

Highly effective contraceptive methods (with a failure rate <1% per year), when used consistently and correctly, include implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or vasectomized partner.

Men who are not vasectomized must agree to use appropriate contraception so as to not impregnate a female partner of reproductive potential during the study and for at least 3 months after the last dose of MTX. Contraception methods include condom use and abstinence.

9.6 Safety/Tolerability, Efficacy and Pharmacokinetic Variables

The Schedule of Assessments is provided in Section 2.1.

9.6.1 Safety/Tolerability 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), pregnancy testing (if applicable), ECGs and AEs of special interest (i.e., IRs, anaphylaxis, gout flares and cardiovascular events).

9.6.1.1 Adjudication and Safety Review Committee

An external Adjudication Committee will be established for this study to adjudicate the AESIs. An internal Safety Review Committee (SRC) will be established to review the aggregate safety data. Subject safety and tolerability of the pegloticase regimen will be discussed and the committee will make a decision as to continue the current treatment regimen or to modify the assigned treatment regimen.

AESIs defined in the protocol (See Section 9.6.1.2.1.5) include IRs, anaphylaxis and cardiovascular events. The AESI of gout flare will not be adjudicated.

The internal Safety Review committee will be comprised of members of the Horizon Clinical Development and Patient Safety and Pharmacovigilance Teams at pre-determined timepoints or ad-hoc dependent on any potential safety signals reported (e.g. anaphylaxis or any SAE related to pegloticase infusion). An independent external Adjudication committee will be established for this study to adjudicate the adverse events of special interest (AESIs) defined in the protocol (See 9.6.1.2.1.5). It will be comprised ofl external experts with experience in immunology, allergic reactions, rheumatology and/or cardiovascular diseases. Details outlining the responsibilities of the adjudication committee will be included in the adjudication committee charter.

Decisions of the committee will be documented and the IRB will be notified if changes to the pegloticase regimen are made. Changes may include, but are not limited to, increasing the pegloticase infusion duration or modifying the methotrexate dosage.

9.6.1.2 Adverse Events

9.6.1.2.1 Definitions

9.6.1.2.1.1 Adverse Event Definition

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

Examples of an AE include:

- Conditions newly detected or diagnosed after the signing of the ICF, including conditions that may have been present but undetected prior to the start of the study
- Conditions known to have been present prior to the start of the study that worsen after the signing of the ICF
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se should not be reported as an AE)

Issues that will not be considered an AE include:

- Conditions present at the start of the study should be recorded as medical history
- Medical or surgical procedures (e.g., endoscopy, appendectomy; however, a condition that leads to a procedure is an AE if it qualifies according to the definitions above)
- Situations where an untoward medical occurrence did not occur (e.g., social, diagnostic, elective, or convenience admission to a hospital)
- Fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not represent a clinically significant change from baseline
- Abnormal laboratory or test findings that are not assessed by the Investigator as a clinically significant change from baseline

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

9.6.1.2.1.2 Serious Adverse Event Definition

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

a. Results in death
b. Is life threatening
   NOTE: The term 'life threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe, prolonged, or untreated.
c. Requires hospitalization or prolongation of existing hospitalization
   NOTE: Hospitalization signifies that the subject has been admitted to the hospital as an inpatient for any length of time. Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of SAEs and not resulting in hospital admission does not qualify for this category, but may be appropriately included in category g (see below). Complications that occur during hospitalization are usually AEs. If a complication prolongs hospitalization or fulfills any other serious criterion, the event will be considered as serious. When in doubt as to whether 'hospitalization' occurred, consult the Sponsor's Medical Monitor.
   Hospitalization will not be considered an AE in and of itself. It will be considered an outcome of an AE. Therefore, if there is no associated AE, there is no SAE. For example, hospitalization for elective or pre-planned treatment of a pre-existing condition that did not worsen from baseline will not be considered an AE.

d. Results in persistent or significant disability/incapacity
   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g., sprained ankle) that may temporarily interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via a medicinal product
g. Is an important medical event
   NOTE: Medical and scientific judgment should be exercised in deciding whether expedited reporting as serious is appropriate in other situations; specifically, important medical events that may not be Immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These should usually be considered serious. Examples of such events are invasive cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. If in doubt as to whether or not an event qualifies as an 'important medical event,' consult the Sponsor's Medical Monitor.

9.6.1.2.1.3 Non-Serious Adverse Event Definition

AEs that do not result in any of the outcomes listed in Section 9.6.1.2.1.2 are considered non-serious.

9.6.1.2.1.4 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.

9.6.1.2.1.5 Adverse Events of Special Interest

AEs of special interest include IRs, anaphylaxis, gout flares and cardiovascular events. AEs of special interest will be collected on a separate eCRF that captures data related to each AE of special interest.

Infusion Reaction

An IR will be defined as any infusion-related AE or cluster of temporally-related AEs, not attributable to another cause, which occur during the pegloticase infusion and for 2 hours post infusion. Other AEs that occur outside of the 2 hour window following the infusion may also be

categorized as an IR at the Principal Investigator's discretion. Signs and symptoms of the IR and treatments administered will be documented in the medical record and in the eCRF. 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 hour following the infusion (e.g., anemia), gout flares, most infectious diseases, or the recurrence or worsening of a known chronic medical problem identified in the subject's medical history.

Anaphylaxis

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives; pruritus or flushing; urticaria and angioedema (of lips, tongue, or uvula) and ≥1 of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    b. Reduced BP 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 BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy, abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that subject (minutes to several hours): systolic BP <90 mmHg or >30% decrease from that subject's baseline

Gout Flares

It is common for potent urate-lowering therapies to lead to acute attacks of gout. Gout flares will be confirmed through questioning or direct observation, detailed in Section 9.6.1.10.

Cardiovascular Events

- The following cardiovascular events will be collected. Major Adverse Cardiovascular Events (MACE) defined as:

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

- Congestive heart failure defined as: hospitalization or prolonged (> 12 hours) emergency department visit due to dyspnea, shortness of breath, with progressive edema accompanied by clinical findings of pulmonary vascular congestion. Radiographic and/or echocardiographic documentation is desirable but not required. Treatment by intravenous (Parenteral) diuretics or inotropes is required to confirm this diagnosis versus ultrafiltration, hemodialysis or left ventricular assist devices.

9.6.1.2.2 Documentation of Adverse Events

AE and 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.

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

9.6.1.2.3 Intensity of Adverse Events

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

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

9.6.1.2.4 Relationship to Study Drug

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

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

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

9.6.1.2.5 Reporting and Documenting SAEs and Product Complaints

9.6.1.2.5.1 Serious Adverse Events

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

reported by submitting the completed SAE form via email or fax to the contact numbers provided below.

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

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

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

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

Follow-up will be obtained via the eCRF, fax, or e-mail, as necessary, until the event resolves or attains a stable outcome. Horizon or designee is responsible for the preparation of MedWatch 3500 A/Council for International Organizations of Medical Sciences I forms and analysis of similar events for individual occurrences (to be submitted as Investigational New Drug [IND] safety letters to the FDA and Investigators according to 21 CFR 312.32 by Horizon).

9.6.1.2.5.2 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.

9.6.1.2.6 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

9.6.1.2.7 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 9.6.1.2.7.

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

9.6.1.2.8 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.

9.6.1.2.9 Reporting of IND Safety Reports

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

9.6.1.2.10 Development Safety Update Reports

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

9.6.1.3 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 and the End of Study/Early Termination Visit. Urine pregnancy tests will also be performed at all other time points, as indicated in the schedule of assessments (Section 2.1)

and results must be confirmed by site personnel prior to any infusion starting. Pregnancy will not be considered an AE in this study, however, any pregnancy complications, including an elective termination for medical reasons, should be reported as an AE.

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

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

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

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

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

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

9.6.1.4 Medical/Surgical History

Medical history, including surgical history, 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.

For subjects with reported allergic history (e.g., seasonal allergies, food allergies, allergies to medications) the Investigator/site should collect additional supplemental information (e.g., severity, current status etc.). In the event of multiple allergies and/or moderate to severe (Grade 2 or higher) allergic history the Investigator should consult with the Medical Monitor prior to enrolling the subject.

9.6.1.5 Vital Signs, Height and Weight

Routine vital signs, including BP, respiratory rate, temperature and heart rate will be measured at Screening, Week -2, Week -4 and at all infusion visits during the Pegloticase + MTX Period and the End of Pegloticase Infusions Visit (if applicable), Week 24/End of Study/Early Termination and 3-month Post-Treatment Follow-up Visit. 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. Subject's arm should be supported at heart level; and cuff placed on the bare arm. A large cuff should be used as needed to fit the upper arm and a consistent arm is to be used at each study visit. The Korotkoff phase V will be used to determine diastolic BP.

During the Pegloticase + MTX Period study visits, vitals should be taken before the pegloticase infusion and any time after the end of the infusion, but prior to subject's discharge/release from the site.

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 and prior to dosing MTX Week -4 Visit; prior to pegloticase infusion on Day 1 and at the Weeks 8, 16 and at the End of Pegloticase Infusions Visit (if applicable), Week 24/End of Study/Early Termination and Month 3 Post-Treatment Follow-up Visits. Height will be collected at the Screening Visit only.

Vital sign monitoring during IR is described in Section 9.5.7.3.2.4.

9.6.1.6 Physical Examinations

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

A targeted physical examination per the investigator judgement but at a minimum should include heart, lungs and abdominal exam and include a joint and skin evaluation and assessment of AEs at Week -4, Week -2, Day 1 and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20 and the End of Pegloticase Infusions Visit (if applicable), Week 24/End of Study/Early Termination and 3-month Post-Treatment Follow-up Visit.

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

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

9.6.1.7 Electrocardiogram

A 12-lead ECG will be performed at Screening for all subjects 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.

9.6.1.8 Clinical Laboratory Safety Tests

Blood (for hematology and clinical chemistry) will be collected at Screening, Week -2, 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 2, Week 6, 14 and 22 Visits, the End -of -Pegloticase -Infusions Visit (if applicable) and Week 24/End -of -Study/Early Termination Visit.

Safety laboratory assessments will include:

3. Hematology: complete blood count with differential (hemoglobin concentration, hematocrit, erythrocyte count, platelet count, leukocyte count and differential leukocyte count);
4. 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 if African American) or 175 x $(S_{cr[\mu mol/L]}/88.4)^{-1.154}$ x $(age)^{-0.203}$x (0.742 if female) x (1.212 if African American), glucose, sodium, potassium, calcium, chloride, total protein, blood urea nitrogen and human chorionic gonadotropin (at the Screening Visit and the Week 24/End of Study/Early Termination Visit for all female subjects of childbearing potential); and
5. 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.

9.6.1.9 Blood Samples for Potential Analysis of Biomarkers

Exploratory inflammatory biomarkers including C-reactive protein levels, in response to pegloticase or other potential treatment for gout may be analyzed. Blood samples for this collection will occur on Day 1, Week 14 and Week 24.

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

9.6.1.10 Assessment of Gout Flare

There is no validated instrument to assess gout flares. Gout flares will be assessed at the time points specified in Section 2.1. Investigators will assess gout flares based on subject questioning and/or direct observation. All gout flares will be recorded as adverse events with the required AE reporting information.

9.6.2 Efficacy Variables

Efficacy will be assessed based on measurement of sUA from blood samples.

9.6.2.1 Serum Uric Acid

Serum samples for measurement of sUA levels will be collected at the Screening Visit, Week -4 and Week -2 Visits during the MTX Run-in Period; within 48 hours prior to each pegloticase infusion (except on Day 1 when only 1 pre-infusion sample is required) and after the end of each pegloticase infusion prior to discharge, from the Pegloticase + MTX Period through Week 22; and at the at the End of Pegloticase Infusion Visit (if applicable); at the Week 24/End of study/Early Termination Visit and Month 3 Visits.

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

If a subject's previous visit pre-infusion sUA (local or central laboratory) is less than 6 mg/dL: it will be allowable to draw the local pre-infusion sUA sample on the day of infusion (and not within 48 prior to infusion) – at the similar time as the sample to send to the central laboratory; however if the prior visit pre-infusion sUA sample was greater than 6 mg/dl (local or central laboratory), a local sUA sample will need to be collected and tested prior to the pegloticase infusion to be certain the subject has not met the stopping rule.

To note: It is allowable for the Local and Central Laboratory sUA samples to be drawn on different days or times so long as both samples are drawn within 48 hours prior to the infusion. A subject with sUA level >6 mg/dL (based on the local or central laboratory) at 2 consecutive study visits, beginning with the Week 2 Visit (not including post-infusion samples), will be discontinued from pegloticase treatment and remain on study.

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

9.6.3 Pharmacokinetic Measurements

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, 12 and 20. An additional PK sample will be collected at the End-of-Study (Week 24)/Early Termination 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.

9.6.4 Anti-drug Antibody Measurements

Immunogenicity of pegloticase will be assessed via serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies. Samples will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 2, 6, 12, 20 and the End of study (Week 24)/Early Termination Visit and 3-month Post-Treatment Follow-up Visits. In the event of an AE suspected to be an IR, a serum sample will be collected at that time or at the subsequent visit for evaluation of pegloticase antibodies.

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.

9.6.5 MTX Polyglutamate Measurements

Blood samples will be collected prior to pegloticase infusion on Day 1, Weeks 14, 22, End of Pegloticase Infusions Visit (if applicable) and 24 Visits during the Pegloticase + MTX Period.

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

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

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Endpoints

9.7.1.1 Primary Endpoint

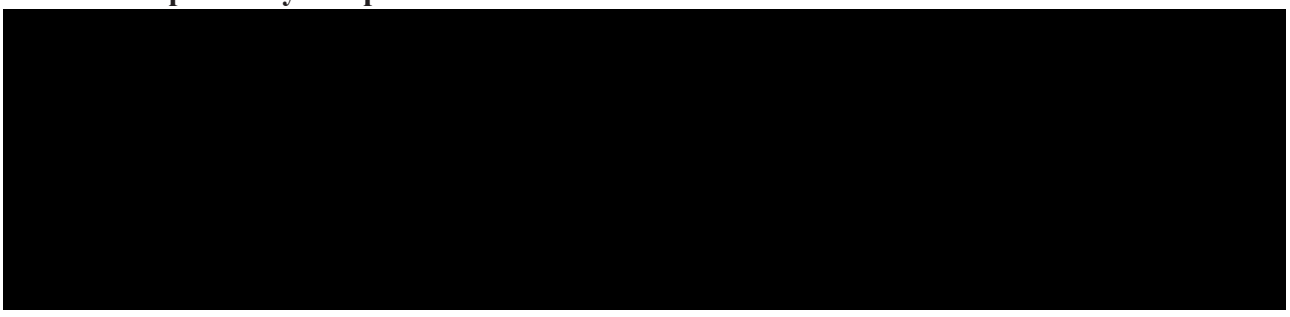
The primary endpoint is the incidence of subjects experiencing IRs (including anaphylaxis) related to pegloticase from Day 1 to Week 24 in the cohort chosen to be the most desirable duration for infusion.

9.7.1.2 Secondary Endpoints

The secondary endpoints will be assessed for the cohort chosen to be the most desirable duration for infusion and include:

- The proportion of Month 6 (Weeks 20, 22 and 24) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.
- The proportion of subjects who experienced any of the following events: IR leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria.
- Time to any of the following events: IR leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria (two consecutive pre-infusion sUAs > 6 mg/dL.

9.7.1.3 Exploratory Endpoints



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9.7.1.4 Pharmacokinetic and Anti-drug Antibody Endpoints

The PK and anti-drug antibody endpoints are:

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

9.7.1.5 Safety Endpoints

Safety endpoints are:

- Incidence of IRs, anaphylaxis, gout flares, cardiovascular events and the AE/SAE profile overall and potentially attributed to the combination of pegloticase and MTX.
- The proportion of subjects who experienced IR leading to slowing down of the infusion rate or discontinuation of treatment.
- The time to first IR leading to slowing down of the infusion rate or discontinuation of treatment.
- Time to first IR.
- The proportion of subjects who were able to complete all infusions over the assigned treatment duration length or a lesser time, without clinically requiring an increased infusion time.
- The proportion of infusions completed over the assigned duration length or a lesser time, without clinically requiring an increased infusion time.
- Laboratory tests.
- Vital signs and physical examinations.

9.7.2 Analysis Sets

The following analysis populations will be defined for this study:

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

9.7.3 Demographics and Baseline Characteristics

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

9.7.4 Subject Disposition

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

In addition, the number and percentage of subjects who completed the pegloticase treatment and who discontinued pegloticase treatment prematurely along with the reasons for discontinuation will be summarized for each analysis set.

9.7.5 Endpoint Analysis

All efficacy analyses will be performed using the mITT set. Baseline characteristics and safety relating to only the MTX Run-in period will be summarized for the ITT set and/or mITT set. All safety analyses relating to pegloticase + MTX period will be summarized using the safety set.

Data will be summarized descriptively by assigned infusion duration regimen, unless otherwise specified. There will be no statistical testing. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum and maximum). Categorical variables will be summarized using frequencies and percentages. Unless otherwise specified, baseline is defined as the last non-missing observation prior to the first dose of MTX.

9.7.5.1 Primary and Secondary Endpoint Analysis

The primary analysis will be performed using the modified intention-to-treat (mITT) population, defined as all enrolled subjects who received ≥1 dose of pegloticase. The primary endpoint is the incidence of subjects experiencing IRs (including anaphylaxis) related to pegloticase from Day 1 to Week 24 in the cohort chosen to be the most desirable duration for infusion (e.g. this may be the 30-minute infusion cohort if infusion-speed limiting criteria not met). The proportion of subjects with an IR (including anaphylaxis) related to pegloticase will be summarized, along

with a 95% exact two-sided (Clopper-Pearson) confidence interval for the proportion. Additionally, this endpoint will be analyzed for each of the other infusion duration cohorts.

The proportion of responders during Month 6 will be summarized, along with a two-sided 95% exact (Clopper-Pearson) confidence interval for the proportion. A responder is defined as a subject for whom the proportion of time that the sUA-time curve is <6 mg/dL during Month 6 (Weeks 20, 22 and 24) is at least 80%. The proportion of time that the sUA level is below 6 mg/dL is defined as the ratio of the time during which the sUA level remains below 6 mg/dL (using linear interpolation, if necessary) to the entire time interval during Month 6.

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

The proportion of subjects experiencing any of the following events: IR leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria (composite endpoint and for each individual component) will be summarized descriptively along with a two-sided 95% exact (Clopper-Pearson) confidence interval.

The time to subjects experiencing any of: IR leading to discontinuation of treatment, anaphylaxis or meeting Individual Subject sUA Discontinuation Criteria will be analyzed both as a composite endpoint and for each individual event. Kaplan Meier (KM) estimates of the time to event will be reported along with the corresponding quartiles and two-sided 95% CI for the median time if there are sufficient number of events to perform the analysis.

9.7.5.2 Exploratory Endpoint Analysis

9.7.6 MTX Polyglutamate and Anti-drug Antibody Analysis

Concentrations of pegloticase and MTX polyglutamate will be summarized by time point using descriptive statistics for the PK and mITT populations, respectively.

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

9.7.7 Safety Analysis

Treatment-emergent AEs (TEAEs) during the Run-In period are defined as events with an onset date on or after the first dose of MTX through the first pegloticase infusion, or 30 days after the last dose of MTX for subjects who do not receive pegloticase. TEAEs during the Pegloticase + MTX Period are defined as events that occur after the start of the first pegloticase infusion through 30 days after the last dose of pegloticase and/or MTX (whichever is later).

TEAEs during the MTX Run-in Period will be summarized with the ITT population and TEAEs during the Pegloticase + MTX Period will be summarized with both the ITT and mITT populations. TEAEs during any period (MTX Run-in Period or Pegloticase + MTX Period) will be summarized for the mITT population. AEs that occur more than 30 days after the last dose of pegloticase and/or MTX through the 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 MTX and pegloticase will also be provided. SAEs and AEs leading to discontinuation of MTX and pegloticase will be presented by system organ class and preferred term.

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

The following safety endpoints will be summarized descriptively along with a two-sided 95% exact (Clopper-Pearson) confidence interval:

- The proportion of subjects who experienced IR leading to slowing down of the infusion rate or discontinuation of treatment.
- The proportion of subjects who were able to complete all infusions over the assigned treatment duration length or a lesser time, without clinically requiring an increased infusion time.
- The proportion of infusions completed over the assigned duration length or a lesser time, without clinically requiring an increased infusion time.

The time to subjects experiencing first IR leading to slowing down of the infusion rate or discontinuation of treatment, and time to subjects first IR will both be analyzed using Kaplan Meier (KM) estimates of the time to event will be reported along with the corresponding quartiles and a 95% CI for the median time if there are sufficient number of events to perform the analysis.

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

Vital signs, including 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.

Data for the MTX Run-in Period and Pegloticase + MTX Period will be summarized separately, where applicable.

9.7.8 Interim Analyses

Safety data will be summarized at the following milestones for safety and tolerability monitoring:

- After 3 subjects complete at least 3 infusions at one assigned infusion duration level.
- After 6 subjects complete at least 3 infusions at one assigned infusion duration level.
- After 10 subjects complete at least 3 infusions at one assigned infusion duration level. Enrollment will be paused from the time the 10th subject is enrolled until after the analysis results are known.
- After 15 subjects complete at least 3 infusions at one assigned infusion duration level if applicable.
- After 20 subjects complete at least 3 infusions at one assigned infusion duration level if applicable.
- After all subjects complete at least 3 infusions.
- Additional safety assessments will be done as needed, for additional subjects enrolled.

The results of these analyses will determine if enrollment will continue at the present infusion duration, or if the assigned duration level should be modified for subsequent subjects.

Final analysis of all data will occur when all subjects have completed the study (including Follow-up visits).

9.7.9 Sample Size and Power Considerations

Initially, cohorts of approximately 10 subjects are planned to be enrolled sequentially at progressively shorter infusion durations beginning with 60-minute infusion duration, progressing down to the 45-minute duration and then to the 30-minute infusion duration. Approximately 110 subjects are planned to be enrolled into the selected infusion cohort. Therefore, the minimum number of subjects enrolling across the 3 different cohorts in the study is approximately 130.

Based on the MIRROR-RCT study, we expect approximately 5.0% of subjects to have an IR (including events of anaphylaxis) when taking pegloticase concurrently with MTX. The sample size of 110 for the selected cohort is chosen to ensure a high probability of ruling out an unacceptably high IR rate. If the observed IR rate is 5%, there is a greater than 80% probability that the upper bound of the two-sided 95% exact confidence interval for the IR rate is less than 13%.

9.8 Changes in the Conduct of the Study

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

The Sponsor's Medical Monitor will consider any requests for exceptions to protocol entry criteria on a case-by-case basis. The Investigator or other health professional in attendance must contact the Sponsor as soon as possible. All protocol deviations and the reasons for such deviations **must** be documented in the eCRF. In the event of a major protocol deviation, the Investigator and Sponsor's Medical Monitor will determine whether the subject should continue to participate in the study.

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

10 SOURCE DOCUMENTATION AND INVESTIGATOR FILES

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

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

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify that the subject meets protocol entry criteria.
- Study number, assigned subject number and verification that written informed consent was obtained (each recorded in dated and signed progress notes).
- Progress notes for each subject visit (each dated and signed).
- Records of each study visit including each study assessment and the identity of the staff member performing the assessment.
- Study drug dispensing and return.

- Review by the Investigator or qualified personnel on the 1572 of laboratory test results.
- AEs (start and stop date, description, action taken and resolution).
- Investigator or sub-investigator's signed assessment of AEs.
- Concomitant medications (start and stop dates, reason for use).
- Condition of subject upon completion of, or premature withdrawal from, the study.

11 CASE REPORT FORMS

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

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

12 STUDY MONITORING

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

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

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

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

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

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

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

13 DATA MANAGEMENT

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

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

14 RETENTION OF RECORDS

No study documents at the study site should be destroyed without prior written agreement between the Sponsor and the Investigator. All subjects' medical records, the Investigator's copy of the eCRF, other supporting data, records of drug dispensing and accountability, signed ICFs, IRB correspondence and correspondence with the Sponsor must be kept by the Investigator for at

least 2 years and/or as required by the local law following the date of the last approval of a marketing application in an ICH region (including the United States) and until there are no pending or contemplated marketing applications in any other ICH region. If an application is not filed or not approved for the indication under study, all study-related files must be retained for at least 2 years and for a period in compliance with all federal, state and local regulations. The Sponsor must be notified prior to the disposal of any study-related files. If the Investigator leaves the practice or institution during the required retention period, it is important that arrangements be made for continued record retention. In that event, the records generally will be retained at the institution at which the study was conducted.

15 PUBLICATION

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

16 REFERENCES

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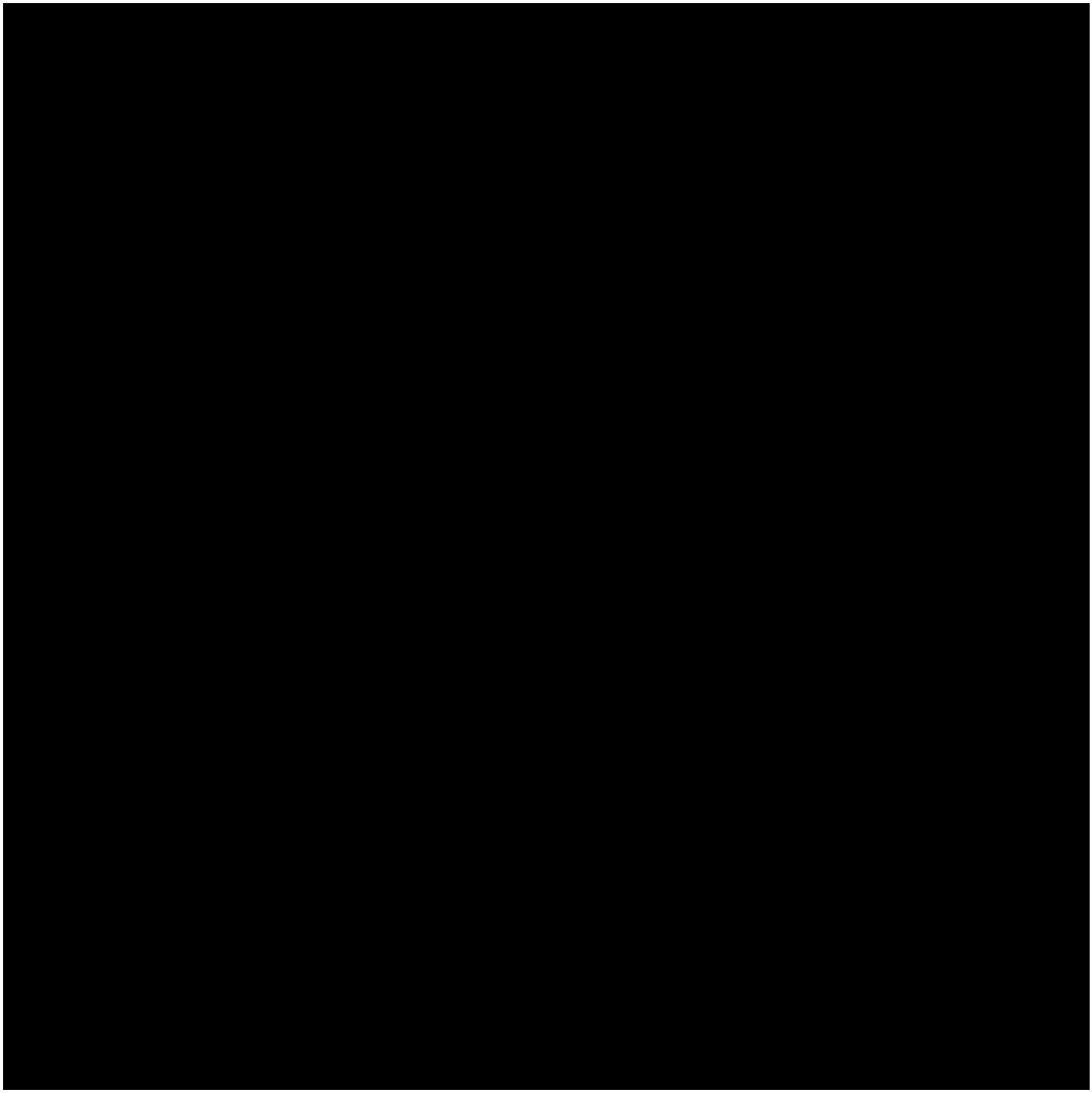
17 APPENDICES

17.1 Administrative Appendix

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

Medical Monitor	[redacted] M.D. Horizon Therapeutics U.S.A., Inc. Two Tower Place, 12th Floor South San Francisco, CA 94080 Mobile telephone number [redacted] Office number: [redacted] Email: [redacted]
Sponsor Representative	[redacted] Sr. Study Manager, Clinical Operations Horizon Therapeutics USA, Inc. 1 Horizon Way Deerfield, IL 60015 Mobile telephone number: [redacted] Fax number: [redacted] Email [redacted]
Sponsor Contact for Serious Adverse Event Reporting	Clinical Safety Fax number: 800-860-7836 Email: clinicalsafety@horizontherapeutics.com
24-hour Phone Contact for Safety Coverage	Med Communications Phone number: 855-479-6742



17.4 Polyethylene Glycol-Conjugated Drug List Appendix

Please refer to this list but understand there may be more Polyethylene Glycol-Conjugated drugs not on this list.

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