CLINICAL TRIAL PROTOCOL FOR KRYSTEXXA

IND: 010122

Protocol Number: HZNP-KRY-408

Version 4.0, Amendment 3

A Phase 4, Open-Label, Multicenter, Efficacy, Safety, Pharmacokinetics and Pharmacodynamics Trial of Intravenous KRYSTEXXA® (pegloticase) Administered Every 4 Weeks with Co-Administration of Weekly Doses of Methotrexate in Patients with Uncontrolled Refractory Gout

(FORWARD Open-Label [OL] Trial)

Short Title: FORWARD OL

Date: 13 April 2022

Sponsor:

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

NCT Number: NCT04762498
This NCT number has been applied to the document
for purposes of posting on Clinicaltrials.gov

PROTOCOL

1 TITLE PAGE

Trial Title:	A Phase 4, Open-Label, Multicenter, E**F**ficacy, Safety, Pharmacokinetics and Pharmacodynamics Trial of Intraven**O**us KRYSTEXXA® (pegloticase) Administe**R**ed Every 4 **W**eeks with Co-Administration of Weekly Doses of Methotrexate in P**A**tients with Uncont**R**olle**D** Refractory Gout (FORWARD Open-Label [OL] Trial)
Protocol Number:	HZNP-KRY-408
Version:	4.0, Amendment 3
Investigational Products:	KRYSTEXXA (recombinant modified mammalian urate oxidase [uricase]); methotrexate (MTX)
Indication:	Chronic gout in adult patients refractory to conventional therapy
Sponsor:	Horizon Therapeutics Ireland DAC 70 St. Stephen's Green Dublin 2 Ireland D02 E2X4
Development Phase:	4
Sponsor's Responsible Medical Officer:	[redacted] MD Senior Medical Director, R&D Clinical Development Horizon Therapeutics U.S.A., Inc. Two Tower Place, 12th Floor South San Francisco, CA 94080
Sponsor Signatory:	[redacted] MD Senior Medical Director, R&D Clinical Development Horizon Therapeutics U.S.A., Inc. Two Tower Place, 12th Floor South San Francisco, CA 94080
Approval Date:	13 April 2022

CONTACT IN THE EVENT OF AN EMERGENCY

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

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

SPONSOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-408

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Protocol Title: A Phase 4, Open-Label, Multicenter, E**F**fficacy, Safety, Pharmacokinetics and Pharmacodynamics Trial of Intraven**O**us KRYSTEXXA® (pegloticase) Administe**R**ed Every 4 **W**eeks with Co-Administration of Weekly Doses of Methotrexate in P**A**tients with Uncont**R**olle**D** Refractory Gout (FORWARD Open-Label [OL] Trial)

Version Date: 13 April 2022

Approved by:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 14-Apr-2022 | 16:48 CDT
[redacted]
[redacted]MS, RAC
[redacted]

14-Apr-2022 | 16:49 CDT

Date

Director, Biostatistics
Biometrics
Horizon Therapeutics USA, Inc.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 14-Apr-2022 | 13:30 CDT
[redacted]
[redacted]MD
[redacted]

14-Apr-2022 | 13:30 CDT

Date

Senior Medical Director
R&D Clinical Development
Horizon Therapeutics USA, Inc.

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-KRY-408

Version: 4.0, Amendment 3

Protocol Title: A Phase 4, Open-Label, Multicenter, E**F**fficacy, Safety, Pharmacokinetics and Pharmacodynamics Trial of Intraven**O**us KRYSTEXXA® (pegloticase) Administe**R**ed Every 4 **W**eeks with Co-Administration of Weekly Doses of Methotrexate in P**A**tients with Uncont**R**olle**D** Refractory Gout (FORWARD Open-Label [OL] Trial)

Version Date: 13 April 2022

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

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

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

Signature:

Name Trial Center Address City State Country	Date

SUMMARY TABLE OF CHANGES

Protocol Version 3.0, Amendment 2 (19 October 2021) to
Protocol Version 4.0, Amendment 3 (13 April 2022)

The table below highlights the primary changes to the Original Protocol. Administrative and typographical updates have also been made. Track changes version of the Protocol Version 4.0, Amendment 3 can be provided on request.

Text Version 3.0, Amendment 2 19 October 2021	Amended Text Version 4.0, Amendment 3 13 April 2022	Reason for Change
Synopsis (Number and Country of Trial Sites) Up to 10 Trial Centers in the United States	**Synopsis (Number and Country of Trial Sites)** Up to 15 Trial Centers in the United States	*Increased potential number of sites to support study enrollment.*
All Objectives To assess the following of up to 2 dose levels of pegloticase (16 mg IV based on prior studies and a possible second dose of 24 mg IV or 32 mg IV, to be determined by review of data from the 16 mg dose group) Q4 Wks co-administered with weekly doses of oral MTX in adult subjects with chronic gout refractory to conventional therapy	**All Objectives** To assess the following of up to 2 dose levels of pegloticase (16 mg IV based on prior studies and a possible second dose level between 24 mg and 32 mg IV) Q4 Wks co-administered with weekly doses of oral MTX in adult subjects with chronic gout refractory to conventional therapy	*Updated to remove the limited scope of data review to be assessed for possible second dose level decision.*
Synopsis (Exploratory Objectives) **8. Trial Objectives** [redacted]	**Synopsis (Exploratory Objectives)** **8. Trial Objectives** *None.*	[redacted]
Synopsis (Trial Design) Assessments will include if any AE/SAEs have occurred within the last 4 weeks and will confirm if any previous AE/SAEs have resolved.	**Synopsis (Trial Design)** Assessments will include occurrence of AE/SAEs within the last 4 weeks and resolution of AE/SAEs ongoing at the ET.	*Administrative change – revision to the language for easier readability.*
Synopsis (Trial Design) **9.4.1 Treatments Administered** *None.*	**Synopsis (Trial Design)** **9.4.1 Treatments Administered** Subjects will not be fasting on the day of infusions and will be encouraged to have a snack or normal meal before or after the infusion.	*Added to clarify non-fasting requirements prior to infusions.*
Synopsis (Trial Design) **9.1 Overall Trial Design and Plan** Serum uric acid stopping criteria will be applied: subjects with sUA level >6 mg/dL at 2 consecutive weekly visits beginning with the Week 1 Visit may discontinue treatment, complete the End of Pegloticase Infusion Visit	**Synopsis (Trial Design)** **9.1 Overall Trial Design and Plan** Serum uric acid stopping criteria will be applied: subjects with sUA level >6 mg/dL at 2 consecutive weekly visits beginning with the Week 1 Visit must discontinue treatment, complete the End of Pegloticase Infusion Visit	*Updated requirement to mandate pegloticase discontinuation criteria if stopping rule is met.*

procedures within 2 weeks, and continue the subject visits according to the protocol (without treatment). The investigator should consult the sponsor's medical monitor to discuss the significance of the sUA values and the potential need to discontinue the subject due to elevations late in the inter-dose interval (third week and fourth week visits, prior to next infusion).	procedures within 2 weeks, and continue the subject visits according to the protocol (without pegloticase treatment).	
Synopsis (Dosage Form and Strength Formulation) **9.4.6.3.1.2 Dose and Administration** If the second cohort will receive 16 mg of pegloticase, it will be administered as an admixture of 16 mg by injecting 2 x 8 mg vials into 50 mL of 0.45% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump. If the second cohort will receive 24 mg of pegloticase, it will be administered as an admixture of 24 mg by injecting 3 x 8 mg vials into 250 mL or 50 mL of 0.9% or 0.45% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump, depending on the infusion duration. If the second cohort will receive 32 mg of pegloticase, it will be administered as an admixture of 32 mg by injecting 4 x 8 mg vials into 250 mL or 50 mL of 0.9% or 0.45% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump, depending on the infusion duration.	**Synopsis (Dosage Form and Strength Formulation)** **9.4.6.3.1.2 Dose and Administration** If the second cohort will receive a higher dose of pegloticase (between 24 and 32 mg), it will be administered as an admixture by injecting required number of 8 mg vials into 50 mL to 250 mL of 0.45% to 0.9% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump (see IP Manual for details).	*Updated to align with the potential dose determination and its preparation.*
Stopping Criteria Subjects with an sUA level >6 mg/dL at 2 consecutive visits beginning with the Week 1 Visit (not including post-infusion samples) may subsequently discontinue pegloticase treatment and can remain in the trial for continued evaluation. Observations 1 and 2 weeks after the first infusion will be prioritized, and sUA values 3 and 4 weeks after each infusion, starting with the Week 3 visit should be discussed between the investigator and the sponsor's medical monitor prior to any decision to discontinue a subject. Subjects with sUA levels >6 mg/dL at Week 3 and Week 4 visits after the last infusion may be allowed to continue infusions if both the Investigator and the Sponsor's medical monitor agree.	**Stopping Criteria** Subjects with an sUA level >6 mg/dL at 2 consecutive visits beginning with the Week 1 Visit (not including post-infusion samples) will discontinue pegloticase treatment and can remain in the trial for continued evaluation.	*Updated requirement to mandate pegloticase discontinuation criteria if stopping rule is met.*

Synopsis (Exploratory Efficacy Enpoints) **9.6.1 Endpoints** [redacted]	**Synopsis (Exploratory Efficacy Endpoints)** **9.6.1 Endpoints** *None*	[redacted]
Synopsis (Statistical Analysis on Efficacy and Safety Parameters) Time from first infusion of pegloticase to the first observed sUA ≥6 mg/dL [redacted] will be summarized using product-limit estimates.	**Synopsis (Statistical Analysis on Efficacy and Safety Parameters)** Time from first infusion of pegloticase to the first observed sUA ≥6 mg/dL [redacted] after first achieving sUA < 6 mg/dL will be summarized using product-limit estimates.	*Revised for accuracy*
Synopsis (Statistical Analysis on Efficacy and Safety Parameters) Duration of sUA <6 mg/dL will be summarized from the time of the first observed sUA value <6 mg/dL until the last observed sUA value <6 mg/dL during the 20-week Q4 Wks pegloticase + MTX treatment period. Subjects whose last sUA value is <6 mg/dL will be censored at the time of the last assessment. The median and quartiles, with associated two-sided 95% confidence intervals, will be calculated.	**Synopsis (Statistical Analysis on Efficacy and Safety Parameters)** *None*	*Removed. Endpoint was replaced with the time to event endpoint.*
Synopsis (Statistical Analysis on Efficacy and Safety Parameters) Once the observations for the first two 4-week periods (i.e., Week 4 and Week 8) have been obtained from approximately the first 10 subjects in the first cohort, the data may be analyzed to determine if 1) an additional 5 subjects should be enrolled at the same dose in the first cohort, 2) > 5 more subjects should be enrolled at the same dose as the first cohort, 3) enrollment in the first cohort should discontinue, and/or 4) enrollment for the second cohort should begin. This determination will be made based on assessment of the available 4- and 8-week pharmacokinetic, pharmacodynamic, efficacy, safety and tolerability data from the approximately first 10 subjects in the first cohort.	**Synopsis (Statistical Analysis on Efficacy and Safety Parameters)** Once the observations for the first two 4-week periods (i.e., Week 4 and Week 8) have been obtained from approximately the first 10 subjects in the first cohort, the data may be analyzed to determine 1) No dose escalation with a) additional subjects enrolled at the same dose in the first cohort, or b) change the infusion duration from 120 minutes to 60 minutes, 2) Dose escalation to between 24 mg and 32 mg Q4 Wks as the second cohort. The infusion duration may change from 120 minutes to 60 minutes; 3) Trial pause and re-evaluation for safety concerns. This determination will be made based on assessment of the available 4- and 8-week PK, PD, efficacy, safety and tolerability data from the approximately first 10 subjects in the first cohort. If additional subjects are enrolled in Cohort 1, determination of the need and the dose for a second cohort will be made based on an additional analysis of available 4- and 8-week PK, PD, efficacy and safety data for all subjects in Cohort 1.	*Revised to account for the possibility of several cohort analyses for one given cohort.*

Synopsis (Sample Size Estimate) **9.6.9 Sample Size and Power Considerations** A sample size of approximately 30 subjects (up to approximately 15 subjects per dose cohort) is planned for this trial. With 15 subjects assessed at a given dose level, an observed response rate for a dichotomous endpoint of 67% (10/15) will provide a two-sided 95% confidence interval with a lower bound of approximately 38%. If 10 subjects are assessed at a given dose level, an observed response rate of 70% (7/10) will provide a two-sided 95% confidence interval with a lower bound of approximately 35%.	**Synopsis (Sample Size Estimate)** **9.6.9 Sample Size and Power Considerations** A sample size of up to 40 subjects (approximately 10-20 subjects per dose cohort) is planned for this trial. With approximately 10 subjects assessed at a given dose level, an observed response rate for a dichotomous endpoint of 70% (7/10) will provide a two-sided 95% confidence interval with a lower bound of approximately 35%. If 20 subjects are assessed at a given dose level, an observed response rate of 70% (14/20) will provide a two-sided 95% confidence interval with a lower bound of approximately 46%.	*Updated the sample size determination statement to account for potential additional subjects to be enrolled in the trial.*
Schedule of Assessments (Footnote 18) Serum samples for measurement of sUA levels will be collected at the Screening Visit, the Week -4 Visit (prior to the first dose of MTX) and the Week -2 Visit during the Run-in Period. On Day 1, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, and Week 48/End of Trial/Early Termination Visit.	**Schedule of Assessments (Footnote 18)** Serum samples for measurement of sUA levels will be collected at the Screening Visit, the Week -4 Visit (prior to the first dose of MTX) and the Week -2 Visit during the Run-in Period. On Day 1, Weeks 1-24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 45, 46, and Week 48/End of Trial/End of PegloticaseVisit. 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.	*Administrative update to align with schedule of assessments succinctly; update to clarify the pre-dose sUA collection requirements (within 48 hours).*
Table 6.1 Imaging Vendor: Bioclinica	**Table 6.1** Imaging Vendor: Clario	*Updated to reflect name change for imaging vendor.*
7.3 Rationale for Dose Selection The 16 mg Q4 Wks regimen is expected to provide therapeutic effect by matching the AUC of the efficacious labeled 8 mg Q2 Wks regimen, with a Ctrough that is half of the 8 mg Q2 Wks regimen. If 16 mg Q4 Wks is well tolerated, but results in sub-optimal sUA responses compared to emerging data for pegloticase with immunomodulators, higher doses to further offset the immunological potential of lower Ctrough levels could be considered. Note that at 24 mg Q4 Wks, a 1.5-fold increase in AUC and 0.8-fold increase in Ctrough compared to 8 mg Q2 Wks is expected and at a dose of 32 mg Q4 Wks, a 2-fold increase in AUC and similar Ctrough to 8 mg Q2 Wks at steady state is expected. Both of these possible doses are well below the no observed adverse effect level (NOAEL) at 10 mg/kg/week observed in the 39-week dog repeat dose safety trial.	**7.3 Rationale for Dose Selection** If 16 mg Q4 Wks is well tolerated but results in sub-optimal sUA responses compared to emerging data for pegloticase with immunomodulators, a higher dose in the range between 24 and 32 mg Q4 Wks to further increase pegloticase exposures may be considered (e.g., 24 mg Q4 Wks to achieve 1.5-fold higher AUC and 20% lower C_{trough} and 32 mg Q4 Wks to achieve 2-fold higher AUC and similar C_{trough}, in comparison to 8 mg Q2 Wks at steady state). Considerations for escalating to a higher dose would be part of a careful safety review of the results with 16 mg Q4 Wks, including PK, safety and sUA profile.	*Updated to align with the potential dose range update that is to be considered for Cohort 2.*

7.3 Rationale for Dose Selection AGILE (HZNP-KRY-403) is a Phase 4, multicenter, open-label, proof-of-concept trial of KRYSTEXXA 8 mg administered IV Q2 weeks over infusion durations of less than 120 minutes on a background of MTX in adult subjects with uncontrolled gout. Approximately 30-50 subjects are to be enrolled. Formal safety reviews have been conducted for the 60- amd 45-minute cohorts. In the 30-minute cohort with 9 subjects currently enrolled…	**7.3 Rationale for Dose Selection** AGILE (HZNP-KRY-403) is an ongoing Phase 4, multicenter, open-label, proof-of-concept trial of KRYSTEXXA 8 mg administered IV Q2 weeks over infusion durations of less than 120 minutes on a background of MTX in adult subjects with uncontrolled gout. Approximately 80-100 subjects are to be enrolled. Formal safety reviews have been conducted for the 60- and-, 45- and 30- minute cohorts. In the currently ongoing 30-minute cohort no unexpected TEAEs, SAEs or AESIs have been observed, and there has been no increased incidence of safety events	*Updated to reflect current status of AGILE trial.*
9.1 Overall Trial Design and Plan The projected potential decision outcomes are as follows: 1.No dose escalation. a. Criteria for this decision include: pegloticase 16 mg Q4 Wks is determined to be safe and well tolerated…. 2. Dose Escalate: … The decision on the choice of dose (24 mg Q4 Wks vs 32 mg Q4 Wks)….	**9.1 Overall Trial Design and Plan** The projected potential decision outcomes are as follows: 1.No dose escalation. a. Additional subjects to be enrolled into Cohort 1 to confirm that pegloticase 16 mg Q4 Wks is safe and well-tolerated… 2. Dose Escalate: … The decision on the choice of dose (between 24 mg Q4 Wks and 32 mg Q4 Wks)…. If the decision outcome from the initial Cohort 1 analysis was to enroll additional subjects into Cohort 1, another Cohort 1 analysis will be performed to establish planned decision for Cohort 2.	*Revised to account for the updated potential dose for Cohort 2; clarified additional cohort 1 analyses if additional subjects are being enrolled in Cohort 1.*
9.3.3.1 Removal of Subjects from Pegloticase Therapy •Lack of Efficacy. (i.e., sUA level >6 mg/dL at 2 consecutive visits beginning with the Week 2 Visit). Note: Observations 1 and 2 weeks after the first infusion will be prioritized, and sUA values 3 and 4 weeks after each infusion, starting with the Week 3 visit should be discussed between the Investigator and the sponsor's medical monitor prior to any decision to discontinue a subject.	**9.3.3.1 Removal of Subjects from Pegloticase Therapy** •Lack of Efficacy. (i.e., sUA level >6 mg/dL at 2 consecutive visits beginning with the Week 1 Visit).	*Updated requirement to mandate pegloticase discontinuation criteria if stopping rule is met.*
9.4.6.2 Determination of Dose Volume Pegloticase will be administered as an admixture of 16 mg (two 8 mg vials), 24 mg (three 8 mg vials) or 32 mg (four 8 mg vials), in 250 mL or 50 mL of 0.9% or 0.45% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion.	**9.4.6.2 Determination of Dose Volume** Pegloticase will be administered as an admixture of 16 mg (two 8 mg vials), or, if a higher dose is selected, it will be administered as an admixture of required number of 8 mg vials in 50mL to 250 mL of 0.45% to 0.9% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion (see IP Manual for details).	*Updated to align with the potential dose determination and its preparation.*

9.4.6.3.1.1 Preparation Aliquots from each of the 2 vials (16mg dose), 3 vials (24mg dose), or 4 vials (32mg dose) vials used will be withdrawn for dose preparation.	**9.4.6.3.1.1 Preparation** Aliquots from each of the vials used will be withdrawn for dose preparation.	*Updated to account for the potential dose range preparation.*
9.5.1.1 Serum Uric Acid A subject with an sUA level >6 mg/dL (based on the local or central laboratory) at 2 consecutive trial visits, beginning with the Week 1 Visit, (not including post-infusion samples) may subsequently discontinue pegloticase + MTX treatment and remain in the trial. Observations 1 and 2 weeks after the first infusion will be more heavily weighted, and sUA values 3 and 4 weeks after each infusion, starting with the Week 3 visit should be discussed between the investigator and the sponsor's medical monitor prior to any decision to discontinue a subject. Subjects with sUA levels > 6 mg/dL at Week 3 and Week 4 visits after the last infusion may be allowed to continue infusions if the both the Investigator and the Sponsor's medical monitor agree.	**9.5.1.1 Serum Uric Acid** A subject with an sUA level >6 mg/dL (based on the local or central laboratory) at 2 consecutive trial visits, beginning with the Week 1 Visit, (not including post-infusion samples) will discontinue pegloticase + MTX treatment and remain in the trial.	*Updated requirement to mandate pegloticase discontinuation criteria if stopping rule is met*
9.5.6 Trial Procedures Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit (not including post-infusion samples) may be subsequently discontinue treatment and remain in the trial. Observations 1 and 2 weeks after the first infusion will be more heavily weighted, and sUA values 3 and 4 weeks after each infusion, starting with the Week 3 visit should be discussed between the investigator and the sponsor's medical monitor prior to any decision to discontinue a subject. Subjects with sUA levels >6 mg/dL at Week 3 and Week 4 visits after the last infusion may be allowed to continue infusions if the both the Investigator and the Sponsor's medical monitor agree.	**9.5.6 Trial Procedures** •Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit (not including post-infusion samples) will discontinue treatment and remain in the trial.	*Updated requirement to mandate pegloticase discontinuation criteria if stopping rule is met*
9.5.6.2 Pegloticase + MTX Period (Prior to Infusion Sections) Within 48 hours of the infusion obtain a local laboratory serum uric acid	**9.5.6.2 Pegloticase + MTX Period (Prior to Infusion Sections)** Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)	*Referenced to clarify pre-dose sUA collection requirements (within 48 hours prior to the infusion)*
9.6.5 Efficacy Endpoint Analysis The number of subjects treated, the number of doses administered and the reason for discontinuing treatment will be summarized by	**9.6.5 Efficacy Endpoint Analysis** *None*	*Administrative change – redundant with what is already described in*

treatment cohort, along with demographics and baseline characteristics.		*Sections 9.6.3, 9.6.4 and 9.6.7.*
9.6.5 Efficacy Endpoint Analysis The number of subjects with at least one adverse event, at least one serious AE, at least one severe AE, and with an AE that leads to discontinuation of pegloticase or premature discontinuation of the trial will be summarized. Adverse events with preferred term will be listed.	**9.6.5 Efficacy Endpoint Analysis** *None*	*Administrative change – moved to 9.6.7 Safety Analysis section.*
9.6.7 Safety Analysis *None*	**9.6.7 Safety Analysis** Extent of exposure of MTX and extent exposure of pegloticase will be summarized for duration of treatment, number of doses administered. Number of interruptions and number of completed infusions with or without interruptions will be summarized for pegloticase. The number of subjects experiencing at least one adverse event, at least one serious AE, at least one severe AE, and with an AE that leads to discontinuation of pegloticase or premature discontinuation of the trial will be summarized.	*Administrative change – moved from 9.6.5 section for accuracy.*
17.1 Administrative Appendix Medical Monitor: [redacted], MD PhD Senior Medical Director Rheumatology Clinical Development Horizon Therapeutics USA, Inc. 1 Horizon Way Deerfield, IL 60015 Mobile telephone number: [redacted] Office telephone number: [redacted] Fax number: [redacted] Email: [redacted]	**17.1 Administrative Appendix** Medical Monitor: [redacted], MD Senior Medical Director R&D Clinical Development 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 Medical Monitor change.*

2 SYNOPSIS

<table>
<tr><td colspan="2">Protocol Title: A Phase 4, Open-Label, Multicenter, EFfficacy, Safety, Pharmacokinetics and Pharmacodynamics Trial of IntravenOus KRYSTEXXA® (pegloticase) AdministeRed Every 4 Weeks with Co-Administration of Weekly Doses of Methotrexate in PAtients with UncontRolleD Refractory Gout (FORWARD Open-Label [OL] Trial)</td></tr>
<tr><td>Protocol Number: HZNP-KRY-408</td><td>Phase: 4</td></tr>
<tr><td>Protocol Version: 4.0, Amendment 3</td><td></td></tr>
<tr><td>Test Drugs: pegloticase, methotrexate (MTX)</td><td>Indication: Chronic gout in adult patients refractory to conventional therapy</td></tr>
<tr><td colspan="2">Number and Country of Trial Sites: Up to 15 Trial Centers in the United States</td></tr>
<tr><td colspan="2">Objectives:
<u>Overall:</u>
The overall objective is to assess the efficacy, safety, pharmacokinetics and pharmacodynamics of up to 2 dose levels of Intravenous (IV) pegloticase infusions at every 4-week (Q4 Wks) intervals up to 6 months (Day 1 - 24 weeks with an optional 24 - 48 weeks) co-administered with weekly oral doses of Methotrexate (MTX), in order to identify an appropriate 4-weekly dose for future clinical trials treating subjects with chronic gout refractory to conventional therapy.
<u>Primary Objective</u>
The primary objective is to choose a dose for further investigation by assessing the effect of up to 2 dose levels of pegloticase administered IV Q4 Wks, co-administered with weekly doses of oral MTX, as measured by the sustained normalization of serum uric acid (sUA) to <6 mg/dL for at least 80% of the time during Month 6 and the duration of sUA to <6 mg/dL over 24 week treatment period in adult subjects with chronic gout refractory to conventional therapy.
<u>Secondary Objectives:</u>
To assess the following of up to 2 dose levels of pegloticase (16 mg IV based on prior studies and a possible second dose level (between 24 mg and 32 mg IV) Q4 Wks co-administered with a weekly dose of oral MTX in adult subjects with chronic gout refractory to conventional therapy:
• Pharmacokinetics
• Pharmacodynamics:
o Proportion of subjects with pre-infusion sUA levels <6 mg/dL
o Area under the sUA concentration vs. time curve from Day 1 to Week 24 and from Day 1 to Week 48.
o Proportion of time subjects sustained sUA <6 mg/dL from Day 1 to Week 24 or Day 1 to Week 48
• Profile of anti-uricase antibodies and anti-poly (ethylene glycol) antibodies
<u>Exploratory Objectives</u>
[redacted]</td></tr>
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[redacted]

Safety & Tolerability Objectives:

To assess the following of up to 2 dose levels of pegloticase (16 mg IV based on prior studies and a possible second dose level (between 24 mg IV and 32 mg IV), Q4 Wks co-administered with weekly doses of oral MTX in adult subjects with chronic gout refractory to conventional therapy:

- Adverse Event (AE)/Serious Adverse Event (SAE) profile overall for the combination of 4-weekly dosing of pegloticase and weekly MTX
    - Incidence of Adverse Events of Special Interest (AESI): Infusion-related reactions, anaphylaxis, gout flares, major adverse cardiovascular events (MACE) including type I and type II non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure
- Laboratory tests: Hematology including complete differential, blood chemistry, and urinalysis
- Vital signs and Physical Examination

Trial Design

The trial design will include 5 to 6 distinct components:

1) a Screening Period (screening should be completed within 35 days prior to Week -4);

2) a 4-week MTX Run-In Period;

3) a 20-week Q4 Wks pegloticase + MTX Treatment Period which includes a Week 24/End of Trial/Early Termination (ET) Visit;

4) an optional extension Q4 Wks pegloticase + MTX Treatment Period from Week 24 to Week 44 if a subject might benefit from additional pegloticase treatment and at the discretion of the Investigator which includes a Week 48/End of Trial/Early Termination Visit;

5) an End of Pegloticase Infusions Visit (if applicable) within 2 weeks following the final infusion if the infusion

is prior to Week 48; and

6) an End of Trial/Week 48/ET Visit. AE/SAE follow-up will occur at the subject's scheduled visit approximately 4 weeks after the last pegloticase infusion.

Those subjects that dose MTX and do not infuse pegloticase (MTX run-in screen failure/s) or ET from the trial for whom 4 weeks of safety follow up is not available will be contacted (Phone/Email), if subject agrees, to assess AE/SAEs approximately 4 weeks post MTX dose or 4 weeks post ET date. Assessments will include occurrence of AE/SAEs within the last 4 weeks and resolution of AE/SAEs ongoing at the ET.

All subjects who meet eligibility criteria at Screening will begin 15 mg MTX orally weekly at the Week -4 visit. Subjects will also take folic acid 1 mg daily dose orally, which may be increased to 2 mg daily dose if the Investigator determines that MTX tolerability is inadequate at 1 mg folic acid. The folic acid daily dose will begin at the MTX Run-In Period (Week -4) and continue until prior to the Week 21 Visit, with an optional extension for an additional 24 (total of 45) weeks at the discretion of the Investigator. The determination to continue on to the optional extension weeks of trial (Weeks 24 through Week 48) will be made by the Investigator in consultation with the subject that it is in the subject's best interest in that the subject's sUA remains adequately controlled, the symptoms of gout remain stable / controlled, the subject is tolerating treatment well and desires to continue pegloticase.

Subjects must be able to tolerate the weekly dose of MTX 15 mg for 4 weeks to be eligible for the Day 1 pegloticase infusion. Subjects who are unable to tolerate the 15 mg dose of MTX during the 4 weeks preceding Day 1 will be considered MTX run-in screen failures.

All subjects who complete the Run-In Period will receive the first pegloticase infusion on Day 1. All subsequent doses and trial visits will be scheduled based on the Day 1 visit date. Subjects will not be fasting on the day of infusions and will be encouraged to have a snack or normal meal before or after the infusion.

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 continues flare prophylaxis per American College of Rheumatology guidelines [FitzGerald JD et al. 2020]. For infusion reaction (IR) prophylaxis, fexofenadine (180 mg orally) will be taken the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) (see Section 9.4.1.3 Infusion Reaction Prophylaxis) 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.

For the first cohort, during the Pegloticase + MTX Period, pegloticase 16 mg will be administered intravenously (IV) every 4 weeks from Day 1 through the Week 20 Visit with an End of Trial Visit at Week 24 for a total of 6 infusions. An optional extension, at the subject and Investigator discretion, will be available for continued infusions through the Week 44 Visit with an End of Trial Visit at Week 48 for a total of up to 12 infusions. Pegloticase will be administered after all pre-dose trial visit assessments have been completed at Day 1 and each Q4 Wk visit. The date and start and stop time of infusion will be recorded.

[redacted]

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

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

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

Samples for measurement of sUA levels, PK analysis of pegloticase, pegloticase immunogenicity and [redacted] 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.

Once the observations for the first two 4-week periods (Week 4 and Week 8) have been obtained from approximately the first 10 subjects in the first cohort, the data may be analyzed to determine if 1) 5 more subjects in the first cohort should be enrolled, 2) > 5 more subjects should be enrolled in the first cohort, 3) enrollment in the first cohort should discontinue, and/or 4) enrollment for a second cohort should begin. This determination will be made based on assessment of the available 4- and 8-week pharmacokinetic (PK), pharmacodynamic (PD), efficacy, safety and tolerability data from the approximately first 10 subjects in the first cohort in concert with Horizon's internal standing FORWARD Trial Data Review Team.

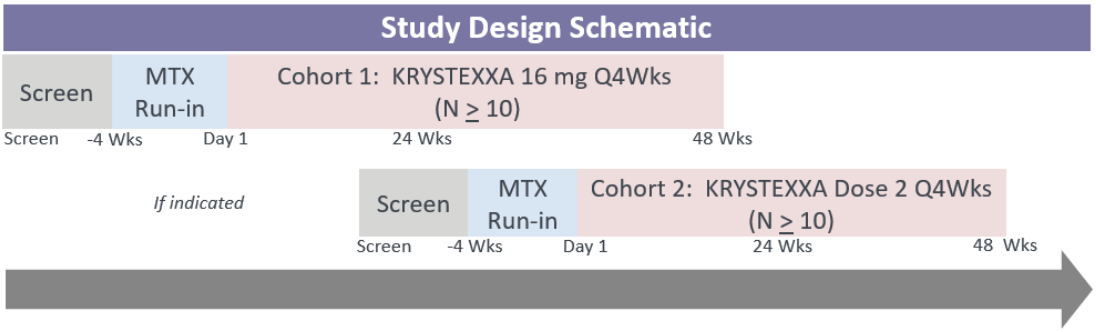
If indicated, the second cohort of subjects will be enrolled once all of the subjects in the first cohort have at a minimum their Week 4 and Week 8 assessments completed. Determination of the need for and the dose for a second cohort will be made based on a preliminary analysis of the efficacy and safety data from the first cohort.

For this second cohort, during the Pegloticase + MTX Period, pegloticase will be administered intravenously (IV) every 4 weeks from Day 1 through the Week 20 Visit for a maximum of 6 infusions over the Week 24 treatment period (Day 1 and Weeks 4, 8, 12, 16, and 20), with an optional extension through the Week 48 visit for a total of up to 12 infusions (at Weeks 24, 28, 32, 36, 40, and 44).

All trial procedures for this cohort will be performed similarly to those for the first cohort (in the exception of the infusion duration, if applicable).

The Horizon trial team will review reported events of infusion reactions, MACE, and anaphylaxis.

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



Subject Population:

Subjects eligible for this trial will have sUA ≥6 mg/dL and gout refractory to conventional therapy characterized by failure to maintain sUA <6 mg/dL despite conventional therapy or contraindication to conventional therapy, and ongoing symptoms of gout including one of the following: visible tophi, recurrent gout flares, or chronic gouty arthropathy.

Inclusion Criteria:

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

1. Willing and able to give informed consent.
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.
3. Adult men or women ≥18 and <80 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 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 as evidenced by either clinical signs consistent with chronic synovitis on clinical examination or the presence of typical gouty erosion(s) on hand and/or foot X-rays
5. Willing to discontinue any oral urate lowering therapy for at least 7 days prior to MTX dosing at Week -4 and remain off while receiving pegloticase treatments.
6. Women of childbearing potential (including those with an onset of menopause <2 years prior to screening, non-therapy-induced amenorrhea for <12 months prior to screening, or not surgically sterile [absence of ovaries and/or uterus]) must have negative serum/urine pregnancy tests during Screening and Week -4; subjects must agree to use 2 reliable forms of contraception during the trial, 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 4 weeks/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.
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 trial, beginning with the initiation of MTX at Week -4 and continuing and for at least 3 months after the last dose of MTX.
8. Able to tolerate MTX 15 mg orally for 4 weeks (Week -4 through Day 1) prior to enrollment.

Exclusion Criteria:

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

1. Weight >160 kg (352 pounds) at Screening.
2. Any serious acute bacterial infection, unless treated and completely resolved with antibiotics at least 2 weeks prior to the Day 1 Visit.
3. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis.
4. Current or chronic treatment with systemic immunosuppressive agents such as MTX, azathioprine, or mycophenolate mofetil; prednisone ≥10 mg/day or equivalent dose of other corticosteroid on a chronic basis (3 months or longer) would also meet exclusion criteria.
5. History of any transplant surgery requiring maintenance immunosuppressive therapy.
6. Known history of hepatitis B virus surface antigen positivity or hepatitis B DNA positivity.
7. Known history of hepatitis C virus RNA positivity, unless treated and viral load is negative.
8. Known history of Human Immunodeficiency Virus (HIV) positivity.
9. Glucose-6-phosphate dehydrogenase deficiency (tested at the Screening Visit centrally or locally).
10. Chronic renal impairment defined as estimated glomerular filtration rate (eGFR) <40 mL/min/1.73 m^2 or currently on dialysis.
11. Non-compensated congestive heart failure or hospitalization for congestive heart failure within 3 months of the Screening Visit, uncontrolled arrhythmia, treatment for acute coronary syndrome (myocardial infarction or unstable angina), or uncontrolled blood pressure (>160/100 mmHg) prior to enrollment at Day 1.
12. Pregnant, planning to become pregnant, breastfeeding, planning to impregnate female partner, or not on an effective form of birth control, as determined by the Investigator.
13. Prior treatment with pegloticase, another recombinant uricase (rasburicase), or concomitant therapy with a polyethylene glycol-conjugated drug.
14. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product.
15. Contraindication to MTX treatment or MTX treatment considered inappropriate.
16. Known intolerance to MTX.
17. Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to MTX administration at Week -4 or plans to take an investigational drug during the trial.
18. Liver transaminase levels (AST or ALT) > 1.25 X 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 <4000/µl, hematocrit <32 percent, or platelet count <75,000/µl.
21. Currently receiving systemic or radiologic treatment for ongoing cancer, excluding non-melanoma skin cancer.
22. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix.
23. Diagnosis of osteomyelitis.
24. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
25. Unsuitable candidate for the trial, 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 trial.
26. Alcohol use in excess of 3 alcoholic beverages per week.
27. A known intolerance to all protocol standard gout flare prophylaxis regimens (i.e., subject must be able to tolerate at least one: colchicine and/or non-steroidal anti-inflammatory drugs and/or low dose prednisone ≤10 mg/day).

28. Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest X-ray may be performed during Screening.

Dose Regimen/Route of Administration:

MTX:

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 (e.g., BID, TID), the total weekly MTX dose should be taken within 24 hours, preferably the same calendar day and the date and time of each dose should be recorded in the dosing calendar. Since subjects will be required to dose MTX within 3 days of each infusion, the day of the week the subject is instructed to dose MTX should be taken into consideration.

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 (e.g., BID, TID).

During the Pegloticase + MTX Periods, MTX should be taken weekly until Week 21 (Week 45 for the optional extension portion of the trial). On weeks prior to infusions, MTX should be taken 1 to 3 days prior to the pegloticase infusion. 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 Periods, if a subject becomes unable to tolerate the MTX the dosage may be decreased.

Subjects will also take folic acid 1 mg (with the option to increase to 2 mg daily at the discretion of the Investigator) orally every day beginning at Week -4 (the start of MTX) until the Week 21 Visit (with an optional extension for an additional 24 (total of 45) weeks at the discretion of the Investigator).

Pegloticase:

For the first cohort, all subjects who meet the inclusion/exclusion criteria and tolerate oral MTX 15 mg weekly during the MTX Run-in Period will be assigned to receive pegloticase at a dose of 16 mg Q4 Wks, as an intravenous infusion every 4 weeks from Day 1 through the Week 20 visit for a total of up to 6 infusions, with an optional extension through the Week 44 visit for a total of up to 12 infusions. All subjects will receive their first infusion at Day 1 and second infusion at the Week 4 Visit followed by Q4 Wks dosing (IV Pegloticase Dose + MTX Periods).

Once the observations for the first two 4-week periods (i.e., Week 4 and Week 8) have been obtained from approximately the first 10 subjects in the first cohort, the data may be analyzed to determine if 1) an additional 5 subjects should be enrolled in the first cohort, 2) > 5 more subjects should be enrolled in the first cohort, 3) enrollment in the first cohort should discontinue, and/or 4) enrollment for the second cohort should begin. This determination will be made based on assessment of the available 4- and 8-week pharmacokinetic, pharmacodynamic, efficacy, safety and tolerability data from approximately the first 10 subjects in cohort 1.

Cohort 2 dose/duration assignment will be determined from the preliminary analysis of the efficacy and safety data from the first cohort. If indicated based on the results of the analysis of the Week 4 and Week 8 data from the first cohort, a second cohort may be assigned to receive either: same dose level but administered over a shorter infusion duration (60 minutes) or a higher dose level of pegloticase but initiated over the initial infusion duration (120 min). If the higher dose is selected and no new safety signals are identified (safety will be continuously monitored by the Horizon internal team), the initial infusion duration (120 min) may be reduced to a shorter infusion duration (60 min) for the remainder of the second cohort. If the shorter infusion duration (60 min) at the increased dose does not remain safe, the determination may be made to increase the infusion duration to the initial duration (120 min).

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 [FitzGerald JD et al. 2020].

Standardized infusion reaction prophylaxis consisting of pre-treatment with an antihistamine, acetaminophen (or alternative) and a corticosteroid will accompany each infusion.

Dosage Form and Strength Formulation (Pegloticase and MTX):

Pegloticase (KRYSTEXXA®) is commercially available in the United States and will be packaged in sterile, single-use 2-mL glass vials with a Teflon®-coated (latex-free) rubber infusion stopper to deliver pegloticase as 8 mg of uricase protein in 1 mL volume. For the first cohort, pegloticase will be administered as an admixture of 16 mg (from two 8 mg vials) in 250 mL of 0.45% or 0.9% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump. Pegloticase will not be administered as an IV push or bolus.

If the second cohort will receive 16 mg of pegloticase, it will be administered as an admixture of 16 mg by injecting 2 x 8 mg vials into 50 mL of 0.45% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump.

If the second cohort will receive a higher dose of pegloticase (between 24 and 32 mg), it will be administered as an admixture by injecting the required number of 8 mg vials into 50 mL to 250 mL of 0.45% to 0.9% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump, depending on the infusion duration (see IP Manual for further details).

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

Duration of Treatment and Follow-up:

Screening: Completed within 35 days prior to the Week -4 visit

MTX Run-in Period (Week -4 through Day 1): 4 weeks of oral MTX for all subjects

Pegloticase + MTX Period (Day 1 through Week 48): MTX dosed weekly and up to 21 weeks with pegloticase infusion visits every 4 weeks with additional non-infusion visits through Week 24, with an optional extension of Q4 Wks Pegloticase + MTX treatment Period from Week 24 to Week 45 and additional non-infusion visits through Week 48 if a subject might benefit from additional pegloticase treatment at the discretion of the Investigator.

End of Pegloticase Infusions Visit (if applicable): If the subject discontinues pegloticase treatment prior to infusions at Week 20 or 44, such as due to the sUA stopping criteria, the subject will complete this visit within approximately 2 weeks of the last infusion. Subjects will continue trial visits.

End of Trial/Early Termination Visit: Week 24 or 48 or earlier if the subject withdraws consent to participate in the trial.

Safety Follow-up at Site/Phone/Email:

AE/SAE follow-up will occur at the subject's scheduled visit approximately 4 weeks after the last pegloticase infusion. Those subjects that dose MTX and do not infuse pegloticase (screen failures) or ET from the trial for whom 4 weeks of safety follow up is not available will be contacted (Phone/Email), if subject agrees, to assess AE/SAEs approximately 4 weeks post MTX dose or 4 weeks post ET date. Assessments will include of any AE/SAEs that have occurred within the last 4 weeks and will 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 4 weeks/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 inquiry will be conducted 3 months after MTX discontinuation regarding partner pregnancy. Note: Subjects that agree to continue study visits post end of pegloticase visit will collect the 4 Wks post treatment follow up as part of the subjects continued visits. In the event a subject continues visits after the end of

pegloticase but the visit is not at least 4 weeks post treatment then the safety follow-up phone call will still be required.
Criteria for Evaluation: Efficacy will be assessed by sUA levels, [redacted]. Patient Reported Disability will be assessed using the [redacted]. The PK of pegloticase will be assessed prior to and after the pegloticase infusion at specified time points. Pegloticase immunogenicity will be assessed by the incidence and titer of anti-PEG and anti-uricase IgG antibodies prior to the pegloticase infusion at specified time points. Safety assessments will include monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations, and monitoring of hematology, blood chemistry and urinalysis.
Stopping Criteria: **Individual Subject Stopping Rule:** Subjects with an sUA level >6 mg/dL at 2 consecutive visits beginning with the Week 1 Visit (not including post-infusion samples) will discontinue pegloticase treatment and can remain in the trial for continued evaluation.

Statistical Analyses:

Primary Efficacy Endpoints

The primary efficacy endpoints are:

1. Proportion of responders at Month 6 (Weeks 20, 21, 22, 23 and 24), defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6
2. Time to first sUA ≥6 mg/dL after first achieving sUA <6 mg/dL, from the first pegloticase infusion until Week 24

Secondary Efficacy Endpoints

The secondary endpoints are:

1. Pharmacokinetic parameters (e.g., AUC, Cmax and C_{trough})
2. Proportion of subjects with pre-infusion sUA <6 mg/dL at each scheduled visit
3. Area under the sUA concentration vs time curve from Day 1 to Week 24 and Day 1 to Week 48
4. Proportion of the subjects sustained sUA< 6 mg/dL from Day 1 to Week 24 and Day 1 to Week 48
5. Proportion of subjects with anti-uricase antibodies and the proportion of subjects with anti-poly (ethylene glycol) antibodies and their titers at each scheduled visit

Exploratory Efficacy Endpoints

Safety and Tolerability Endpoints

1. Adverse Events:
2. Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) regardless the relationship to trial drug and relationship, each
3. Incidence of TEAEs leading to trial drug discontinuation
4. Incidence of AESI: IRs, anaphylaxis, gout flares, and MACE including type I and type II non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure
5. Laboratory tests: changes in laboratory test results from baseline at each scheduled visit
6. Vital signs: changes from baseline at each scheduled visit

Statistical Analysis on Efficacy and Safety Parameters

All subjects enrolled (i.e., ITT Analysis Set) will be used to assess efficacy endpoints. The estimand for the primary analysis will use the Treatment Policy Strategy for most intercurrent events; selected intercurrent events leading to data that are missing completely at random may be addressed with a While-on-Treatment Strategy.

The number of subjects treated, the number of doses administered and the reason for discontinuing treatment will be summarized by treatment cohort, along with demographics and baseline characteristics.

The proportion of time each subject's sUA is <6 mg/dL will be calculated using observed data during Month 3 (Weeks 10, 11, 12, 13, and 14), Month 6 (Weeks 20, 21,22, 23, and 24), Month 9 (Weeks 32, 34, and 36), and Month 12 (Weeks 44, 46, and 48). The amount of time that sUA is <6 mg/dL (using linear interpolation if necessary) will be calculated, and divided by the total amount of time from the first to the last observed sUA value in corresponding time range (missed values in this time range will be ignored for purposes of this calculation). Subjects who have no available sUA value in this time range will be imputed as non-responders unless the data are missing completely at random, in which case they will be omitted from the analysis. Two-sided exact 95% confidence intervals will be calculated.

Time from first infusion of pegloticase to the first observed sUA ≥6 mg/dL or [redacted] after first achieving sUA < 6 mg/dL will be summarized using product-limit estimates. Subjects who never have an observed sUA value ≥6 mg/dL or two consecutive time will be censored at the time of their last observed sUA value. The median and quartiles, with associated two-sided 95% confidence intervals, will be calculated.

The proportion of subjects with sUA value <6 mg/dL at each scheduled assessment will be summarized. Subjects who have no available sUA value at a given scheduled assessment will be imputed as non-responders unless the data are missing completely at random, in which case they will be omitted from the analysis. Two-sided exact 95% confidence intervals will be calculated.

The area under the sUA curve from Day 1 to Week 24 and from Day 1 to Week 48 will be summarized using linear interpolation between observed data points.

One-at-a-time 95%, two-sided confidence intervals will be calculated for each parameter. No adjustment will be made for multiple endpoints or multiple time points.

The number of subjects with at least one adverse event, at least one serious AE, at least one severe AE, and with an AE that leads to discontinuation of pegloticase will be summarized. Adverse events with preferred term will be listed.

Data will be summarized on a regular basis for purposes of planning future cohorts, with no Type I error rate adjustments made due to multiple summaries.

Once the observations for the first two 4-week periods (i.e., Week 4 and Week 8) have been obtained from approximately the first 10 subjects in the first cohort, the data may be analyzed to determine 1) No dose escalation with a) additional subjects enrolled at the same dose in the first cohort, or b) change the infusion duration from 120 minutes to 60 minutes, 2) Dose escalation to between 24 mg and 32 mg Q4 Wks as the second cohort. The infusion duration may change from 120 minutes to 60 minutes 3) Trial pause and re-evaluation for safety concerns. This determination will be made based on assessment of the available 4- and 8-week PK, PD, efficacy, safety and tolerability data from the approximately first 10 subjects in the first cohort. If additional subjects are enrolled in Cohort 1, determination of the need and the dose for a second cohort will be made based on an additional analysis of available 4- and 8-week PK, PD, efficacy and safety data for all subjects in Cohort 1.

Sample Size Estimate:

A sample size of up to 40 subjects (approximately 10-20 subjects per dose cohort) is planned for this trial.

With approximately 10 subjects assessed at a given dose level, an observed response rate for a dichotomous endpoint of 70% (7/10) will provide a two-sided 95% confidence interval with a lower bound of approximately 35%. If 20 subjects are assessed at a given dose level, an observed response rate of 70% (14/20) will provide a two-sided 95% confidence interval with a lower bound of approximately 46%.

2.1 Schedule of Assessments

	Screen[1]	MTX Run-in Period[2]		Section 1 Pegloticase + MTX Period[3] Day 1 through Week 24 (For optional Weeks 24-48 see section 2)																	
	Screen Visit	(-4wk ±3 d)	(-2wk ±3 d)	**Day 1	Wk1 (±1 d)	Wk2 (±1 d)	Wk3 (±1 d)	Wk4 (±3 d)	Wk5 (±1 d)	Wk6 & Wk7 (±1 d)	Wk8 (±3 d)	Wk9, Wk10 & Wk11 (±1 d)	Wk12 (±3 d)	Wk13, Wk14 & Wk15 (±1 d)	Wk16 (±3 d)	Wk17, Wk18 & Wk19 (±1 d)	Wk20 (±3 d)	Wk21 (±1 d)	Wk22 (±1 d)	Wk 23 (±1 d)	Wk24 (±3 d)
Trial Procedure/ Assessment				**Inf: 1**				**Inf: 2**			**Inf: 3**		**Inf: 4**		**Inf: 5**		**Inf: 6**				**EOT**
Informed consent	X																				
Enrollment				X																	
Demographic data	X																				
Inclusion/ exclusion criteria	X	X	X	X																	
Medical/Gout/ surgical /substance use history[4]	X																				
Medication use history[5]	X																				
Chest, hand/foot X-ray[6]	X																				
Physical examination[7]	X	X		X				X			X		X		X		X				X

	Screen[1]	**MTX Run-in Period[2]**		**Section 1 Pegloticase + MTX Period[3] Day 1 through Week 24 (For optional Weeks 24-48 see section 2)**																
	Screen Visit	**(-4wk ±3 d)**	**(-2wk ±3 d)**	****Day 1**	**Wk1 (±1 d)**	**Wk2 (±1 d)**	**Wk3 (±1 d)**	**Wk4 (±3 d)**	**Wk5 (±1 d)**	**Wk6 & Wk7 (±1 d)**	**Wk8 (±3 d)**	**Wk9, Wk10 & Wk11 (±1 d)**	**Wk12 (±3 d)**	**Wk13, Wk14 & Wk15 (±1 d)**	**Wk16 (±3 d)**	**Wk17, Wk18 & Wk19 (±1 d)**	**Wk20 (±3 d)**	**Wk21 (±1 d)**	**Wk22 (±1 d)**	**Wk 23 (±1 d)**	**Wk24 (±3 d)**
Trial Procedure/ Assessment				**Inf: 1**				**Inf: 2**			**Inf: 3**		**Inf: 4**		**Inf: 5**		**Inf: 6**				**EOT**
Vital signs, height, and weight[8]	X	X		X				X			X		X		X		X				X
Electro-cardiogram[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	X	X
Concomitant medications[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Document gout flares and intensity	X	X		X				X			X		X		X		X				X
[redacted]	[redacted]	[redacted]		[redacted]				[redacted]					[redacted]				[redacted]				[redacted]
[redacted]	[redacted]	[redacted]		[redacted]				[redacted]					[redacted]				[redacted]				[redacted]
[redacted]		[redacted]		[redacted]									[redacted]								[redacted]
MTX dosing calendar		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MTX dosing[12]		Once Weekly beginning at Week -4 to one week after the last infusion																			

	Screen[1]	MTX Run-in Period[2]		Section 1 Pegloticase + MTX Period[3] Day 1 through Week 24 (For optional Weeks 24-48 see section 2)																
	Screen Visit	**(-4wk ±3 d)**	**(-2wk ±3 d)**	****Day 1**	**Wk1 (±1 d)**	**Wk2 (±1 d)**	**Wk3 (±1 d)**	**Wk4 (±3 d)**	**Wk5 (±1 d)**	**Wk6 & Wk7 (±1 d)**	**Wk8 (±3 d)**	**Wk9, Wk10 & Wk11 (±1 d)**	**Wk12 (±3 d)**	**Wk13, Wk14 & Wk15 (±1 d)**	**Wk16 (±3 d)**	**Wk17, Wk18 & Wk19 (±1 d)**	**Wk20 (±3 d)**	**Wk21 (±1 d)**	**Wk22 (±1 d)**	**Wk 23 (±1 d)**	**Wk24 (±3 d)**
Trial Procedure/ Assessment				**Inf: 1**				**Inf: 2**			**Inf: 3**		**Inf: 4**		**Inf: 5**		**Inf: 6**				**EOT**
MTX dispensing[12]		Dispense MTX through EDC **only**. Dispense as needed																		
Gout prophylaxis Rxs filled[13]		Rxs filled as needed																		
Fexofenadine Rx filled[14]		Rxs filled as needed																		
Folic acid Rx filled[15]		Rxs filled as needed																		
MTX compliance/ reconciliation		X	X	X				X			X		X		X		X				X
Infusion reaction prophylaxis[16]				X				X			X		X		X		X				X
IR prophylaxis compliance (Yes/No)				X				X			X		X		X		X				X
Folic acid/gout flare prophylaxis compliance Yes/No)		X	X	X				X			X		X		X		X				X

	Screen[1]	**MTX Run-in Period[2]**		**Section 1 Pegloticase + MTX Period[3] Day 1 through Week 24 (For optional Weeks 24-48 see section 2)**																
	Screen Visit	**(-4wk ±3 d)**	**(-2wk ±3 d)**	****Day 1**	**Wk1 (±1 d)**	**Wk2 (±1 d)**	**Wk3 (±1 d)**	**Wk4 (±3 d)**	**Wk5 (±1 d)**	**Wk6 & Wk7 (±1 d)**	**Wk8 (±3 d)**	**Wk9, Wk10 & Wk11 (±1 d)**	**Wk12 (±3 d)**	**Wk13, Wk14 & Wk15 (±1 d)**	**Wk16 (±3 d)**	**Wk17, Wk18 & Wk19 (±1 d)**	**Wk20 (±3 d)**	**Wk21 (±1 d)**	**Wk22 (±1 d)**	**Wk 23 (±1 d)**	**Wk24 (±3 d)**
Trial Procedure/ Assessment				**Inf: 1**				**Inf: 2**			**Inf: 3**		**Inf: 4**		**Inf: 5**		**Inf: 6**				**EOT**
Pegloticase infusion				X				X			X		X		X		X				
Pegloticase PK sampling[17]				X	X	X	X	X		X	X				X				X		X
[redacted]																					
sUA[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology sample	X	X	X	X		X		X			X		X		X		X				X
Clinical chemistry sample	X	X	X	X		X		X			X		X		X		X				X
Spot urine collection				X									X								X
hs-CRP	X			X									X								X
Anti-Drug Antibody sample (ADA)[19]				X		X		X			X				X						X

	Screen[1]	**MTX Run-in Period[2]**		**Section 1 Pegloticase + MTX Period[3] Day 1 through Week 24 (For optional Weeks 24-48 see section 2)**																
	Screen Visit	**(-4wk ±3 d)**	**(-2wk ±3 d)**	****Day 1**	**Wk1 (±1 d)**	**Wk2 (±1 d)**	**Wk3 (±1 d)**	**Wk4 (±3 d)**	**Wk5 (±1 d)**	**Wk6 & Wk7 (±1 d)**	**Wk8 (±3 d)**	**Wk9, Wk10 & Wk11 (±1 d)**	**Wk12 (±3 d)**	**Wk13, Wk14 & Wk15 (±1 d)**	**Wk16 (±3 d)**	**Wk17, Wk18 & Wk19 (±1 d)**	**Wk20 (±3 d)**	**Wk21 (±1 d)**	**Wk22 (±1 d)**	**Wk 23 (±1 d)**	**Wk24 (±3 d)**
Trial Procedure/ Assessment				**Inf: 1**				**Inf: 2**			**Inf: 3**		**Inf: 4**		**Inf: 5**		**Inf: 6**				**EOT**
Additional samples for future analysis [20]		X		X									X								X
G6PD test (Local or Central Lab)	X																				
Pregnancy test[21]	X	X	X	X				X			X		X		X		X				X
PI assessment of subject clinical status and subject treatment goals[22]	X																				X

	Section 2 Optional Pegloticase + MTX Period[3] (optional Week 24 through Week 48 for subjects that consent/elect to further treatment)													**End of Pegloticase Infusions Visit[24] (if applicable)**	**End of Trial/ Early Termination**	**Safety Follow-up Phone/ Email Visit**	**MTX Partner Pregnancy Follow-up**
	W24 (±3 d)	**W26 (±3 d)**	**Wk 28 (±3 d)**	**Wk 30 (±3 d)**	**Wk 32 (±3 d)**	**Wk 34 (±3 d)**	**Wk 36 (±3 d)**	**Wk 38 (±3 d)**	**Wk 40 (±3 d)**	**Wk 42 (±3 d)**	**Wk 44 (±3 d)**	**Wk 45 (±3 d)**	**Wk 46 (±3 d)**	**Within 2 weeks following final infusion if prior to Wk 44**	**Wk 48 (±3 d)**	**4 Wks after last pegloticase infusion or MTX dose (±3 d)**	**approx. 3 months after last MTX dose**
Trial Procedure/ Assessment	**Inf: 7**		**Inf: 8**		**Inf: 9**		**Inf: 10**		**Inf: 11**		**Inf: 12**						
Physical examination[7]	X						X							X	X		
Vital signs, height, and weight[8]	X		X		X		X		X		X			X	X		
AE/SAE assessment[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Document gout flares and intensity	X		X		X		X		X		X			X	X		
[redacted]	[redacted]						[redacted]							[redacted]	[redacted]		
[redacted]	[redacted]						[redacted]							[redacted]	[redacted]		
[redacted]	[redacted]						[redacted]							[redacted]	[redacted]		
MTX dosing calendar	X	X	X	X	X	X	X	X	X	X	X	X	X				
MTX dosing[12]	Once Weekly beginning at Week -4 to one week after the last infusion																
MTX dispensed[12]	Dispense MTX through EDC only. Dispense as needed																

	Section 2 Optional Pegloticase + MTX Period[3] (optional Week 24 through Week 48 for subjects that consent/elect to further treatment)													**End of Pegloticase Infusions Visit[24] (if applicable)**	**End of Trial/ Early Termination**	**Safety Follow-up Phone/ Email Visit**	**MTX Partner Pregnancy Follow-up**
	W24 (±3 d)	**W26 (±3 d)**	**Wk 28 (±3 d)**	**Wk 30 (±3 d)**	**Wk 32 (±3 d)**	**Wk 34 (±3 d)**	**Wk 36 (±3 d)**	**Wk 38 (±3 d)**	**Wk 40 (±3 d)**	**Wk 42 (±3 d)**	**Wk 44 (±3 d)**	**Wk 45 (±3 d)**	**Wk 46 (±3 d)**	**Within 2 weeks following final infusion if prior to Wk 44**	**Wk 48 (±3 d)**	**4 Wks after last pegloticase infusion or MTX dose (±3 d)**	**approx. 3 months after last MTX dose**
Trial Procedure/ Assessment	**Inf: 7**		**Inf: 8**		**Inf: 9**		**Inf: 10**		**Inf: 11**		**Inf: 12**						
Gout prophylaxis Rxs filled[13]	Rxs filled as needed																
Fexofenadine Rx filled[14]	Rxs filled as needed																
Folic acid Rx filled[15]	Rxs filled as needed																
MTX compliance/ reconciliation	X		X		X		X		X		X			X	X		
Infusion reaction prophylaxis[16]	X		X		X		X		X		X						
IR prophylaxis compliance (Yes/No)	X		X		X		X		X		X						
Folic acid/gout flare prophylaxis compliance (Yes/No)	X		X		X		X		X		X			X	X		
Pegloticase infusion	X		X		X		X		X		X						
Pegloticase PK sampling[17]	X						X							X	X		

	Section 2 Optional Pegloticase + MTX Period[3] (optional Week 24 through Week 48 for subjects that consent/elect to further treatment)													**End of Pegloticase Infusions Visit[24] (if applicable)**	**End of Trial/ Early Termination**	**Safety Follow-up Phone/ Email Visit**	**MTX Partner Pregnancy Follow-up**
	W24 (±3 d)	**W26 (±3 d)**	**Wk 28 (±3 d)**	**Wk 30 (±3 d)**	**Wk 32 (±3 d)**	**Wk 34 (±3 d)**	**Wk 36 (±3 d)**	**Wk 38 (±3 d)**	**Wk 40 (±3 d)**	**Wk 42 (±3 d)**	**Wk 44 (±3 d)**	**Wk 45 (±3 d)**	**Wk 46 (±3 d)**	**Within 2 weeks following final infusion if prior to Wk 44**	**Wk 48 (±3 d)**	**4 Wks after last pegloticase infusion or MTX dose (±3 d)**	**approx. 3 months after last MTX dose**
Trial Procedure/ Assessment	**Inf: 7**		**Inf: 8**		**Inf: 9**		**Inf: 10**		**Inf: 11**		**Inf: 12**						
[redacted]	[redacted]						[redacted]										
sUA[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X						X							X	X		
Clinical chemistry	X						X							X	X		
Spot urine collection	X						X							X	X		
hs-CRP	X						X							X	X		
Antibody testing[19]	X						X							X	X		
Additional samples for future analysis[20]	X						X							X	X		
Pregnancy test[21]	X		X		X		X		X		X			X	X	X	
PI assessment of subject clinical status and subject treatment goals[22]	X													X	X		
Partner pregnancy[23]																	X

AE = adverse event; d = day(s); EDC = electronic data capture; Inf = infusion; G6PD = glucose-6-phosphate dehydrogenase; [redacted]; hs-CRP = high-sensitivity C-reactive protein; IR = infusion reaction; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; PK = pharmacokinetic; Rx = prescription; sUA = serum uric acid; V= Visit; wk(s) = week(s)

** Day 1 is the baseline visit for all visit windows.

Footnotes:

1. The Screening Visit can occur any time within 35 days prior to the first dose of MTX at Week -4.
2. At the Week -4 visit, subjects will receive MTX 15 mg orally weekly. Subjects will continue to take the MTX during the Run-in Period (from Week -4 to Day 1) at the 15 mg MTX dose. If a subject does not tolerate the 15 mg MTX dose after the Week -4 Visit and prior to Day 1, the subject will be considered a screen failure. If the subject screen fails, the subject should be contacted approximately 4 weeks after the last dose to assess AE/SAEs.
3. 24-Week Pegloticase + MTX Period; followed by additional, optional 24-weeks (for a total of 48-weeks) Pegloticase + MTX Period
4. The Investigator or designee will collect a complete gout history and other relevant medical/surgical/substance use history.
5. Medication history will be collected at Screening. History of all prior gout medications will be collected. History of non-gout medication use in the year prior to Screening will be collected.
6. Subjects that do not have a chest X-ray within 2 years prior to Screening will have an X-ray done during Screening, if deemed necessary by the Investigator. Subjects that do not have a hand/foot X-ray prior to Screening may have an X-ray done during Screening to confirm Inclusion Criterion 4, if deemed necessary by the Investigator.
7. A complete physical examination will be performed at the Screening Visit, including assessment of HEENT, heart, lungs, abdomen, skin, extremities, neurological status and musculoskeletal including an assessment for the presence of tophi. A targeted physical examination per investigator judgement will be conducted at Week -4, Day 1, and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20, 24, 36 and the non-infusion End of Pegloticase Infusions Visit (if applicable), and Week 48/End of Trial/Early Termination; at a minimum this should include heart, lungs, and abdominal exam. Clinically significant findings from the targeted physical examinations will be recorded as AEs.
8. Routine vital signs, including blood pressure, respiratory rate, temperature, and heart rate will be measured at Screening, Week -4, Day 1 and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and the End of Pegloticase Infusions Visit (if applicable), Week 48/End of Trial/Early Termination. Heart rate and blood pressure measurements should be taken after the subject has been in a sitting position and in a rested and calm state with proper positioning including back support, feet flat on the floor, for at least 5 minutes. Subject's arm should be supported at heart level; and cuff placed on the bare arm. A large cuff should be used as needed to fit the upper arm and a consistent arm is to be used at each trial visit. The Korotkoff phase V will be used to determine diastolic blood pressure. During the Pegloticase + MTX Period trial 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. 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, 24, 36 and at the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 48/End of Trial/Early Termination. Height will be collected at the Screening Visit only.
9. Electrocardiogram should be completed during Screening. The Electrocardiogram is read at the site. When possible, a 12-lead ECG will also be performed at the time if an AESI of infusion reaction, anaphylaxis and MACE is suspected.
10. AE/SAE follow-up and Concomitant Medication data collection will occur at the subject's scheduled visit or if spontaneously reported approximately 4 weeks after the last pegloticase infusion. For those subjects that dose MTX and do not infuse pegloticase or ET from the trial for whom 4 weeks of safety follow up is not available will be contacted (Phone/Email) if subject agrees, to assess AE/SAEs approximately 4 weeks post MTX dose or 4 weeks post ET date. Assessments will include of any AE/SAE's that have occurred within the last 4 weeks and confirm if any previous AE/SAEs have resolved. Note: Subjects that agree to continue study visits post end of pegloticase visit will collect the 4 Wks post treatment follow up as part of the subjects continued visits. In the event a subject continues visits after the end of pegloticase but the visit is not at least 4 weeks post treatment then the safety follow-up phone call will still be required. 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 4 weeks/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 each AE, the Investigator will be asked to record if the event was possibly an infusion reaction or anaphylaxis and if so, will be prompted to complete additional eCRFs.

[redacted]

MTX must be taken ≥60 minutes prior to each pegloticase infusion. The last dose of MTX will be taken one week after the subject's last 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 continues flare prophylaxis throughout the pegloticase treatment per American College of Rheumatology guidelines [FitzGerald JD et al.2020].
14. For IR prophylaxis, fexofenadine (180 mg orally) will be taken the day before and the morning of just prior to each infusion.
15. Subjects will take folic acid 1 or 2 mg (2 mg only if deemed necessary by the Investigator) orally every day beginning at Week -4 (the start of MTX) until one week after the last infusion at Week 21, Week 45 or End of Pegloticase/End of Trial/Early Termination.
16. Infusion reaction prophylaxis includes fexofenadine (180 mg orally) administered the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) (see 9.4.1.3Infusion Reaction Prophylaxis) administered on the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, immediately prior to each infusion.
17. For all subjects, serum samples for PK analysis will be collected after the end of infusion on Day 1 (prior to discharge); at Week 1, Week 2, Week 3, prior to the pegloticase infusion and after the end of infusion (prior to discharge) at the Weeks 4; at Week 6 and Week 7, prior to the pegloticase infusion and post the infusion at weeks 8 and 16, at Week 22 and prior to and post the pegloticase infusion at week 24 (unless the subject is not entering the optional Section 2 then no post-infusion sample is required for subjects at Week 24), and prior to and post the pegloticase infusion at Week 36. Additional PK samples will be collected at non-infusion visits: End of Pegloticase infusion Visit and Week 48/End of Trial/Early Termination visits.
18. Serum samples for measurement of sUA levels will be collected at the Screening Visit, the Week -4 Visit (prior to the first dose of MTX) and the Week -2 Visit during the Run-in Period. On Day 1, Weeks 1-24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 45, 46, and Week 48/End of Trial/End of Pegloticase Visit. On infusion visit dates a pre-dose and post dose sUA will be collected to be shipped to the Central laboratory. See the Laboratory Manual for instructions. In the event of an AE suspected to be an infusion reaction, a serum sample will be collected at that time or at the subsequent visit for evaluation of pegloticase antibodies. If for any reason the week prior to each infusion, central laboratory sUA data is not received or compromised, a local laboratory sample will need to be resulted prior to the infusion to be certain the subject has not met the stopping criteria. 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.
19. Serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 2, 4, 8, 16, 24, 36; and at the non-infusion End of Pegloticase Infusions Visit (if applicable) or the Week 48/End of Trial/Early Termination
20. For subjects who provide consent, optional urine and blood samples will be collected from each consenting subject prior to the first dose of MTX at Week -4, prior to the infusion at Day 1 and Weeks 12, 24, 36 and the End of Pegloticase Infusions Visit (if applicable) and the Week 48/End of Trial/Early Termination.
21. For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit. A urine pregnancy test will be performed prior to each infusion and approximately 4 weeks after the last MTX dose if the subject has not ovulated; at the End of Pegloticase Infusions Visit (if applicable), the Week 48/End of Trial/Early Termination Visit. 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 4 weeks/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.
22. The Investigator will review the clinical status and individual subject treatment goals at Screening, Week 24, and the End of Pegloticase Infusions Visit (if applicable) or the Week 48/End of Trial/Early Termination Visit (See Appendix 17.4)
23. Subjects who are non-vasectomized males will be asked 3 months after MTX discontinuation regarding partner pregnancy. This will occur by phone/email visit.
24. Subjects who end treatment due to the stopping criteria or other reasons should complete the End of Pegloticase Treatment Visit within 2 weeks of the last infusion. Subjects should remain on the trial. See full Protocol Section 9.3.3.1.1 for details on visits and procedures.

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
G6PD	Glucose-6-Phosphate Dehydrogenase
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
HIV	Human Immunodeficiency Virus
hs-CRP	high-sensitivity C-Reactive Protein
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
IR	infusion reaction
IRB	Institutional Review Board
IV	intravenous(ly)
LLN	lower limit of normal
MACE	major adverse cardiovascular events
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PO	oral
pUA	plasma uric acid

Abbreviation	**Definition**
RNA	ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sUA	serum uric acid
ULN	upper limit of normal
ULT	urate lowering therapy
USP	United States Pharmacopeia
Wk/s	Week/s

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

5 ETHICS

5.1 Institutional Review Board/Independent Ethics Committee

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

5.2 Ethical Conduct of the Trial

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

5.3 Subject Information and Consent

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

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

The ICF and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the 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 trial 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 trial contain a section for documenting all subject ICFs, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the ICF should be reviewed and updated, if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised ICF, and give their consent to continue in the trial.

5.4 Compensation for Health Damage of Subjects/Insurance

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

5.5 Confidentiality

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

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

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

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

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

6 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

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

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

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

Table 6.1 Table of Non-Sponsor Trial Responsibilities

Trial Responsibility	Organization
Clinical drug supply and distribution	PCI Pharma Services 4545 Assembly Drive Rockford, IL 61109
Central safety laboratory	Labcorp Central Laboratory Services LP 8211 SciCor Drive Indianapolis, IN 46214
Data Management	Medidata 350 Hudson Street, 9th Floor New York, NY 10014
Clinical Research Organization	Labcorp Central Laboratory Services LP 8211 SciCor Drive Indianapolis, IN 46214
Central imaging vendor	Clario 211 Carnegie Center Drive Princeton, NJ 08540

7 INTRODUCTION

7.1 Background

7.1.1 Gout

Gout affects approximately 4% of the United States population, is the most common form of inflammatory arthritis in men, and is associated with decreased quality of life [Saag and Choi, 2006; Singh and Strand, 2008; Zhu et al, 2011; Sattui et al, 2014]. The frequency of gout is increasing worldwide, with prevalence rates estimated to be as high as 7% in older men [Mikuls et al, 2005; Saag and Choi, 2006; Roddy and Doherty, 2010]. While the exact prevalence is unknown, as many as 200,000 persons in the United States experience chronic symptoms of gout, which is sometimes referred to as chronic refractory gout, despite trials of oral urate-lowering therapy. This is characterized by ongoing symptoms of active disease and a failure to control/maintain serum uric acid (sUA) <6 mg/dL with conventional xanthine oxidase inhibitors (i.e., allopurinol and febuxostat) and uricosuric agents (i.e., probenecid) [AAC Briefing Document 2009; Brook et al, 2010; Wertheimer et al, 2013; Khanna et al, 2016].

These patients often have significant, disabling urate deposits in soft tissues and bone known as tophi.

7.1.2 Pegloticase

Pegloticase (KRYSTEXXA), a recombinant modified mammalian urate oxidase [uricase]), is indicated for treatment-failure gout (TFG) to control hyperuricemia and to manage the signs and symptoms of gout. Pegloticase was granted orphan designation by the FDA on 21 February 2001 (ODA #00-1356) and pegloticase 8 mg every two weeks was approved by the FDA on 14 September 2010 for the treatment of adult patients with chronic gout refractory to conventional therapy. Pegloticase 8 mg every four weeks was also assessed in the pivotal phase 3 trials but this dosing regimen is not included in the KRYSTEXXA product label.

In a phase 1 trial in 24 patients with symptomatic gout, subjects received single 1-hour intravenous infusions of 0.5, 1, 2, 4, 8 or 12 mg pegloticase (Sundy 2007). Pegloticase exposure increased approximately proportionally to dose. Plasma UA levels decreased with increasing pegloticase dose or concentrations. All doses were well tolerated; adverse events were mild to moderate, with gout flares being most common.

The plasma UA lowering potential of pegloticase was evaluated in a phase 2 dose ranging trial in 41 subjects with symptomatic gout (Sundy 2008). Doses evaluated were 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks and 12 mg every 4 weeks. More than 50% of subjects were responders, maintaining plasma UA concentrations ≤6 mg/dL for at least 80% of the treatment period. The highest percentage of responders was observed in the 8 mg every 2 weeks group (88%). Gout flares occurred in 88% of patients. The majority of adverse events, other than gout flare, were unrelated to treatment and mild to moderate in severity. Infusion-day adverse events were the most common reason for trial withdrawal (12 of 15). There were no anaphylactic reactions.

Two replicate pivotal phase 3 studies for pegloticase were undertaken to establish the efficacy and safety of the product. Twelve biweekly intravenous infusions containing either pegloticase 8 mg at each infusion (every 2 weeks dosing group), pegloticase alternating with placebo at successive infusions (every 4 weeks dosing group), or placebo (placebo group) (Sundy et al., 2011). 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 2 weeks was 42%, that for the pegloticase 8 mg every 4 weeks was 35%, versus a placebo response rate of 0%. There was also a greater reduction in complete resolution of ≥ 1 tophus in the every 2 weeks, but not the every 4 weeks dosing group, and favorable effect of pegloticase treatment in the reduction of the number of tender and swollen joints in both the every 2 weeks and the every 4 weeks dosing group. Taken together, these data suggest that pegloticase 8 mg every 4 weeks is a minimally effective dose. In subsequent open-label extension studies, pegloticase led to continued control of plasma uric acid (pUA), reduction in gout flares, and continued resolution of tophi, suggesting continuing benefit with extended pegloticase treatment beyond the initial 6 months of therapy, particularly in subjects who met responder criteria in the placebo-controlled trials.

In the phase 3 pivotal studies, deaths, AEs, SAEs, as well as the laboratory abnormalities were generally equally distributed across placebo and pegloticase treatment groups, with the clear exception of gout flares and infusion reactions. Pegloticase treated subjects exhibited a higher rate of gout flares during Months 1-3 as uric acid was being acutely lowered, then a decrease in gout flares vs. placebo during Months 4-6. Despite use of prophylactic medications against hypersensitivity including administration of corticosteroids, antihistamine, and acetaminophen in advance of each pegloticase infusion, infusion reactions were seen in 22/85 (26%) subjects receiving the 8 mg every 2 weeks regimen, as compared to 35/84 (42%) subjects in the 8 mg every 4 weeks regimen and 2/43 (5%) in the placebo group. There was no specified definition of anaphylaxis in the Phase 3 protocols, and there was no investigator reported events of anaphylaxis in the Phase 3 studies with pegloticase. However, in a post-hoc review applying the NIAID/FAAN criteria (Sampson et al., 2006), it was determined that across the Phase 2 and Phase 3 program, anaphylaxis occurred in 6.5% of subjects treated with pegloticase dosed every 2 weeks. Anaphylaxis generally occurred within 2 hours after treatment. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. All of these events had relatively rapid resolution with the cessation of infusion.

In a post-hoc analysis, the apparent role of immunogenicity in both loss of urate lowering effect and incidence of infusion reactions was appreciated. Only 2% of subjects with anti pegloticase antibody titers exceeding 1:2430 maintained a urate-lowering response to pegloticase compared with 63% of subjects who were treated for at least 2 months without developing high-titer antibodies ($p < 0.001$) (Sundy et al., 2011). The incidence of IRs was higher among subjects who developed high-titer antibodies compared with those who had titers that did not exceed 1:2430 (60% vs 19%; $p < 0.001$) (Sundy et al., 2011). In addition, most IRs occurred when sUA levels were greater than 6 mg/dL. Retrospective analyses showed that the loss of urate-lowering efficacy, as reflected by sUA of greater than 6 mg/dL, preceded a patient's first IR, whenever it occurred, in 20 (91%) of 22 subjects treated with pegloticase every 2 weeks (Calabrese et al, 2017).

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). This trial will attempt to mitigate the loss of sUA response to pegloticase by the pre-treatment and concomitant use of MTX with pegloticase.

Because of the limited treatment options for patients with uncontrolled gout, immunomodulators have been co-administered with pegloticase in an effort to prevent anti-drug antibody formation and increase the length of effective pegloticase therapy, similar to what is done in other rheumatic diseases treated with biologicals (Krieckaert et al, 2012; Lie et al, 2015). The successful use of immunomodulators (MTX, azathioprine, leflunomide and cyclosporine) with pegloticase, in patients who received pegloticase treatment for the first time, is supported by case reports that examined different immunomodulatory agents with varying doses, schedules and routes given prior to the start of pegloticase (Hershfield et al, 2014; Berhanu et al, 2017; Freyne 2018; Albert et al, 2020; Botson and Peterson, 2019; Bessen et al, 2019a; Bessen et al, 2019b; Rainey et al, 2020; Masri et al, 2020). In case reports of MTX with pegloticase, the proportion of

responders (based on each case's definition) was 100% (10/10 patients) (Botson and Peterson, 2019), 100% (7/7 patients) (Bessen et al, 2019a; Bessen et al, 2019b) and 80% (8/10 patients) (Albert et al, 2020); these responder rates are higher than the 42% rate observed in early Phase 3 clinical trials of pegloticase alone (Sundy et al, 2011). Similar to results of case studies, a recent prospective open-label clinical trial reported that a high proportion of patients treated concomitantly with MTX (oral 15 mg/week started 4 weeks prior to the first dose of pegloticase and throughout the pegloticase treatment period) maintained therapeutic response to pegloticase at 6 months (79% [11/14]) (Botson et al, 2020).

Altering the dosing regimen for pegloticase has been employed in an attempt to decrease the frequency of anti-pegloticase antibody development. Examination of pegloticase pharmacokinetics indicated that the 8 mg every 2 weeks regimen might not maintain sufficiently high levels of the enzyme during the first month of therapy (Lipsky 2014), possibly contributing to immunogenicity. This hypothesis was tested in a multicenter open-label trial in which patients received one of several different dosing regimens. The initial dose was 8 mg for all patients <120 kg in body weight and 8, 12, or 16 mg for those ≥120 kg. Subsequent dosing was 8 mg on weeks 1 and 2, followed by 8 mg every 2 weeks through week 16 for a total of 10 doses. Of the 36 patients who have completed the treatment regimen with data fully analyzed at the time of this writing, 19 (52.8%) were responders (Saag 2017; Saag 2018). All regimens were well tolerated in a cohort of gout patients with eligibility criteria similar to the current trial.

In the current trial, less frequent (i.e., every 4 weeks) regimens are being assessed to identify an every 4 weeks dose that achieves a similar efficacy and safety profile as the currently approved 8 mg every 2 weeks regimen, in order to inform further clinical evaluations. In this context, 16 mg every 4 weeks is a reasonable first step, as this will provide similar total exposure (AUC) as 8 mg every 2 weeks (over a total 4-week interval) and half of the C_{trough}. Preliminary data from the TRIPLE trial have shown that a loading dose of 16 mg, followed by 8 mg on Week 2 and 3, then 8 mg every 2 weeks through Week 17 for a total of 10 doses was well tolerated in a cohort of gout patients with eligibility criteria similar to this trial [IND 127668, NCT 02598596)] (Saag 2017).

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:	$\{[H_3C\text{-}O\text{-}(CH_2CH_2\text{-}O)_m\text{-}CO\text{-}]_n\text{-}NH\text{-}$ **[TYKKNDEVEF VRTGYGKDMI KVLHIQRDGK YHSIKEVATT VQLTLSSKKD YLHGDNSDVI PTDTIKNTVN VLAKFKGIKS IETFAVTICE HFLSSFKHVI RAQVYVEEVP WKRFEKNGVK HVHAFIYTPT GTHFCEVEQI RNGPPVIHSG IKDLKVLKTT QSGFEGFIKD QFTTLPEVKD RCFATQVYCK WRYHQGRDVD FEATWDTVRS IVLQKFAGPY DKGEYSPSVQ KTLYDIQVLT LGQVPEIEDM EISLPNIHYL NIDMSKMGLI NKEEVLLPLD NPYGKITGTV KRKLSSRL]**$\}_4$ Wherein, m=~225, n=~10.2 and each uricase monomeric subunit having the amino acid sequence listed above. Approximately 10.2 units of methoxypoly (ethylene glycol) are attached to Lysine(K) residues per uricase monomeric subunit.
Appearance:	Clear colorless solution, free of visible particles.

7.1.2.2 Safety Pharmacology

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

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

The results from the acute and chronic toxicity studies did not indicate any toxic or adverse effect of pegloticase administration. The AUC and C_{max} exposure margins at the 10 mg/kg/week IV no observed adverse effect level in the 39-week dog trial is approximately 50- and 40-fold, respectively, greater than the projected exposure at the highest proposed clinical dose of 32 mg q4w.

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

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

7.1.2.3 Non-clinical Pharmacokinetics

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

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

7.1.2.4 Pharmacokinetics

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

Following single IV infusions of 0.5 mg to 12 mg pegloticase in 23 subjects 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 subjects undergoing hemodialysis (Trial 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 trial drug was not removed by the dialysis process.

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

7.1.2.5 Risks of Pegloticase

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

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

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

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

Since IRs can occur, all subjects will receive pre-treatment prophylaxis consisting of an antihistamine, acetaminophen, and a corticosteroid prior to each infusion of pegloticase. To standardize this regimen, subjects will receive fexofenadine (180 mg orally) the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, immediately prior to each infusion. Please refer to Section 9.4.1.3 Infusion Reaction Prophylaxis for further details.
The risk of anaphylaxis and IRs is higher in patients whose sUA level increases to >6 mg/dL. Beginning with Week 1, subjects with sUA level >6 mg/dL at 2 consecutive trial visits will be classified as a non-responder, with observations 1 and 2 weeks after each infusion prioritized

over sUA values 3 and 4 weeks after each infusion. These subjects may discontinue from treatment but remain on trial.

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

7.1.3 Methotrexate Overview and Risks

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

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

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

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

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

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

7.2 Rationale for this Trial

The currently approved dosing regimen for KRYSTEXXA, 8 mg infused IV over 2 hours every 2 weeks, requires a substantial commitment of time from gout patients as well as substantial utilization of infusion center resources. Therefore, less frequent (i.e., every 4 weeks) regimens are being assessed in this trial to identify an every 4 week dose that achieves a similar efficacy and safety profile that is similar to the currently approved 8 mg every 2 week regimen, to inform further clinical evaluations. Some subjects who, in the judgement of the Investigator, may benefit from additional pegloticase treatment may receive optional monthly dosing for an additional 6 infusions for a total of 48 weeks. The development of anti-drug antibodies can be influenced by drug and treatment-related factors, as well as patient characteristics. A potential

prophylactic strategy to manage anti-drug antibody response with pegloticase is the co-administration of immunomodulatory therapy. Various methods are used to reduce antibody production in other settings, the most common of which is the use of traditional rheumatoid arthritis disease-modifying drugs, such as MTX, azathioprine, mycophenolate mofetil, leflunamide, and others, as is commonly implemented with rheumatoid arthritis biological therapy (e.g., infliximab and other infusible and subcutaneous antibody products) [Strand et al, 2017].

MTX is the most commonly used non-biological disease modifying agent worldwide and is frequently used in combination with other biological therapies [Strand et al, 2017]. There is also early, open label data suggesting that MTX may effectively mitigate the immune response with pegloticase (Botson et al, 2020; Albert et al, 2020). Therefore, in the current trial, pegloticase + MTX will be employed to mitigate IRs with pegloticase when administered every 4 weeks.

7.3 Rationale for Dose Selection

The current, labelled dose of pegloticase (KRYSTEXXA®) is 8 mg Q2 Wks, with a well-established benefit/risk relationship. In the pivotal Phase 3 trials of pegloticase, the data in aggregate revealed 8 mg Q4 Wks to have had inferior efficacy and safety compared to 8 mg Q2 Wks: it provides half the total exposure (AUC) and a quarter of the trough plasma concentration (C_{trough}) compared to 8 mg Q2 Wks and led to lesser resolution of clinical tophi and lower aggregate response rates with greater gout flare rates and greater IR rates compared to Q2w dosing. Thus in the pivotal trials, pegloticase 8 mg Q4 Wks appeared to be a minimally effective dose and is not included in the dosing and administration sections of the current product label.

For this trial, 16 mg Q4 Wks is a reasonable first step, as this will provide similar AUC as 8 mg Q2 Wks (over a 4 Week interval) and half of the C_{trough}. Preliminary data had shown that a loading dose of 16 mg followed by 8 mg on Week 2 and 3, then 8 mg every 2 weeks through Week 17 for a total of 10 doses was well tolerated in gout patients whose characteristics were similar to those described by the eligibility criteria for the current trial [IND 127668, NCT 02598596)].

If 16 mg Q4 Wks is well tolerated but results in sub-optimal sUA responses compared to emerging data for pegloticase with immunomodulators, a higher dose in the range between 24 and 32 mg Q4 Wks to further increase pegloticase exposures may be considered (e.g., 24 mg Q4 Wks to achieve 1.5-fold higher AUC and 20% lower C_{trough} and 32 mg Q4 Wks to achieve 2-fold higher AUC and similar C_{trough}, in comparison to 8 mg Q2 Wks at steady state). Considerations for escalating to a higher dose would be part of a careful safety review of the results with 16 mg Q4 Wks, including PK, safety and sUA profile.

Currently, pegloticase is FDA approved for intravenous administration over no less than 120 minutes [KRYSTEXXA Full Prescribing Information]. 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.

AGILE (HZNP-KRY-403) is an ongoing Phase 4, multicenter, open-label, proof-of-concept trial of KRYSTEXXA 8 mg administered IV Q2 weeks over infusion durations of less than 120 minutes on a background of MTX in adult subjects with uncontrolled gout. Approximately 80-100 subjects are to be enrolled. The treatment period with KRYSTEXXA is approximately 24 weeks. Cohorts of approximately 10 subjects are being enrolled sequentially at progressively shorter infusion durations, beginning with a 60-minute infusion duration, progressing to a 45-minute and then to a 30-minute infusion duration. Formal safety reviews are being conducted after all subjects reach their 3rd infusion at each infusion duration. Formal safety reviews have been conducted for the 60-, 45- and 30- minute cohorts.

Since the database cutoff date, no unexpected TEAEs, SAEs or AESIs have been observed in the the 60-minute cohort which included 10 subjects and the 45-minute cohort which included 13 subjects. In the currently ongoing 30-minute cohort, no unexpected TEAEs, SAEs or AESIs have been observed, and there has been no increased incidence of safety events.

8 TRIAL OBJECTIVES

Overall:

The overall objective is to assess the efficacy, safety, pharmacokinetics and pharmacodynamics of up to 2 dose levels of Intravenous (IV) pegloticase infusions at every 4-week (Q4 Wk) intervals up to 6 months (Day 1 - 24 weeks with an optional 24 - 48 weeks) co-administered with weekly oral doses of Methotrexate (MTX), in order to identify an appropriate 4-weekly dose for future clinical trials treating subjects with chronic gout refractory to conventional therapy.

Primary Objective

The primary objective is to choose a dose for further investigation by assessing the effect of up to 2 dose levels of pegloticase administered IV Q4 Wks, co-administered with weekly doses of oral MTX, as measured by sustained normalization of serum uric acid (sUA) to <6 mg/dL for at least 80% of the time during Month 6 and the duration of sUA to <6 mg/dL over 24-week treatment period in adult subjects with chronic gout refractory to conventional therapy.

Secondary Objectives

To assess the following of up to 2 dose levels of pegloticase (16 mg IV and a possible second dose between 24 mg and 32 mg IV), Q4W co-administered with weekly doses of oral MTX in adult subjects with chronic gout refractory to conventional therapy:

- Pharmacokinetics
- Pharmacodynamics:
    - Proportion of subjects with pre-infusion sUA levels <6 mg/dL
    - Area under the sUA concentration vs. time curve from Day 1 to Week 24 and from Day 1 to Week 48.

- Proportion of time subjects sustained sUA <6 mg/dL from Day 1 to Week 24 or Day 1 to Week 48

- Profile of anti-uricase antibodies and anti-poly (ethylene glycol) antibodies

Exploratory Objectives

Safety & Tolerability Objectives:

To assess the following of up to 2 dose levels of pegloticase (16 mg IV and a possible second dose between 24 mg and 32 mg IV) Q4W co-administered with weekly doses of oral MTX in adult subjects with chronic gout refractory to conventional therapy:

- Adverse Event (AE)/Serious Adverse Event (SAE) profile overall for the combination of 4-weekly dosing of pegloticase and weekly MTX
    - Incidence of Adverse Events of Special Interest (AESI): Infusion-related reactions, anaphylaxis, gout flares, and MACE including type I and type II non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure
- Laboratory tests: Hematology including complete differential, blood chemistry, and urinalysis
- Vital signs and Physical Examination

9 INVESTIGATIONAL PLAN

9.1 Overall Trial Design and Plan

The trial design will include 5 to 6 distinct components: 1) a Screening Period (screening should be completed within 35 days prior to Week -4); 2) a 4-week Run-In MTX Period; 3) a 20-week Q4 Wks pegloticase + MTX Treatment Period which includes a Week 24/End of Trial/Early Termination (ET) Visit; 4) an optional extension Q4 Wks pegloticase + MTX Treatment Period from Week 24 to Week 44 if a subject might benefit from additional pegloticase treatment and at the discretion of the Investigator which includes a Week 48/End of Trial/Early Termination Visit; 5) an End of Pegloticase Infusions Visit (if applicable) within 2 weeks following the final infusion if the infusion is prior to Week 48; and 6) an End of Trial/Week 48/ET Visit. AE/SAE follow-up will occur at the subject's scheduled visit approximately 4 weeks after the last pegloticase infusion. Those subjects that dose MTX and do not infuse pegloticase (screen failure/s) or ET from the trial for whom 4 weeks of safety follow up is not available will be contacted (Phone/Email), if subject agrees, to assess AE/SAEs approximately 4 weeks post MTX dose or 4 weeks post ET date. Assessments will include if any AE/SAE's have occurred within the last 4 weeks and will confirm if any previous AE/SAEs have resolved.

All subjects who meet eligibility criteria at Screening will begin 15 mg MTX orally weekly at the Week -4 visit. Subjects will also take folic acid 1 mg daily dose orally, which may be increased to 2 mg daily dose if the Investigator determines that MTX tolerability is inadequate at 1 mg. The folic acid daily dose will begin at the MTX Run-In Period (Week -4) and continuing until prior to the Week 21 Visit, with an optional extension for an additional 24 (total of 45) weeks at the discretion of the Investigator.

Subjects must be able to tolerate the weekly dose of MTX 15 mg for 4 weeks to be eligible for the Day 1 pegloticase infusion. Subjects who are unable to tolerate the 15 mg dose of MTX during the 4 weeks preceding Day 1 will be considered MTX run-in screen failures.

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

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 continues flare prophylaxis per American College of Rheumatology guidelines [FitzGerald JD et al. 2020] For infusion reaction (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.

For the first cohort, during the Pegloticase + MTX Period, pegloticase 16 mg will be administered intravenously (IV) every 4 weeks from Day 1 through the Week 20 Visit with an End of Trial Visit at Week 24 for a total of 6 infusions. An optional extension, at the subject and Investigator discretion, will be available for continued infusions through the Week 44 Visit with an End of Trial Visit at Week 48 for a total of up to 12 infusions. Pegloticase will be administered after all pre-dose trial visit assessments have been completed at Day 1 and each Q4 Wk visit. The date and start and stop time of infusion will be recorded. Serum uric acid stopping criteria will be applied: subjects with sUA level >6 mg/dL at 2 consecutive weekly visits beginning with the Week 1 Visit will discontinue treatment (complete the End of Pegloticase Infusion Visit procedures within 2 weeks, and continue the subject visits according to the protocol (without treatment). sUA levels will be collected prior to and post infusion on the day of all infusions as well as weekly at each non-infusion visit until Week 24 then bi-weekly during the optional duration of the trial (Week 24 though Week 48). Given that the sUA may rise towards the end of the Q4 interval simply due to the pharmacokinetics of pegloticase rather than necessarily indicating a loss of efficacy due to formation of Anti-Drug Antibodies (ADA), the 1- and 2-week post infusion values will be prioritized for the purpose of the stopping criteria.

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 stopping 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 MTX, the MTX dose may be reduced and/or discontinued based on pre-defined criteria, and the subject may remain in the trial.

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

After the End of Trial/ET/Week 24/Week 48 Visit (or End of Pegloticase Infusion Visit [if applicable]), subjects should resume regular care for gout per the judgment of the treating physician, including resumption of ULT upon pegloticase discontinuation, if appropriate.

Samples for measurement of sUA levels, PK analysis of pegloticase, pegloticase immunogenicity and [redacted] 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.

Once the observations for the first two 4-week periods (Week 4 and Week 8) have been obtained from approximately the first 10 subjects in the first cohort, the data may be analyzed to determine if 1) 5 more subjects in the first cohort should be enrolled, 2) > 5 more subjects should be enrolled in the first cohort, 3) enrollment in the first cohort should discontinue, and/or 4) enrollment for a second cohort should begin. This determination will be made based on assessment of the available 4- and 8-week pharmacokinetic, pharmacodynamic, efficacy, safety and tolerability data from the approximately first 10 subjects in the first cohort.

If indicated, the second cohort of subjects will be enrolled once all of the subjects in the first cohort have at a minimum their Week 4 and Week 8 assessments completed. Determination of the need for and the dose for a second cohort will be made based on a preliminary analysis of the efficacy and safety data from the first cohort.

The FORWARD Trial Data Review Team will evaluate the overall safety and tolerability of the 16 mg Q4 Wks regimen with a focus on any potential hypersensitivity reactions including infusion reactions and anaphylaxis, the pattern of serum uric acid concentrations (the primary efficacy outcome variable) with a view to the adequacy of sUA lowering, and the pharmacokinetics of pegloticase to compare observed data in this trial with those in other clinical trials. That is, safety and sUA pattern (a PD marker as well as the efficacy endpoint across 12 and 24 weeks) would be considered primarily alongside the PK profile.

The projected potential decision outcomes are as follows:

1. No dose escalation.
    a. Additional subjects to be enrolled into Cohort 1 to confirm that pegloticase 16 mg Q4 Wks is safe and well-tolerated, with sUA lowering effects and a safety profile similar to the expectation for pegloticase 8 mg Q2 Wks with immunomodulatory concomitant treatment (Botson et al, 2020; Khanna P et al, 2020 Abstract; Khanna P et al, 2020 Oral Presentation).
    b. No dose escalation but change in the infusion rate - shorten the duration of infusion from 120 minutes to 60 minutes. The decision to shorten the duration of infusion would take into consideration the pattern of sUA lowering actually observed, as well as the tolerability profile. In addition, in order to mitigate potential infusion-reaction related events due to shortened infusion, the volume of the prepared infusion solution will be decreased from a total of 250 mL to a total of 50 mL.
2. Dose Escalate: Pegloticase 16 mg Q4 Wks appears to be safe and well-tolerated, but sUA lowering effects appear sub-optimal compared to expectations for pegloticase 8 mg Q2 Wks with immunomodulatory concomitant therapy.

The decision on the choice of dose (between 24 mg and 32 mg Q4 Wks) would take into consideration the pattern of sUA lowering actually observed, as well as the tolerability profile. For example, if the C_{trough} immunogenic potential is not offset by the use of the methotrexate immunomodulator concomitant treatment, an early rise in sUA above the 6 mg/dL threshold would be expected, particularly at early time points such as week 1 and post infusion.

a. If the higher dose is selected and no new safety signals are identified (safety will be continuously monitored by the Horizon internal team), the initial infusion duration (120 min) may be reduced to a shorter infusion duration (60 min) for the remainder of the second cohort. If the shorter infusion duration (60 min) at the increased dose does not remain safe, the determination may be made to increase the infusion duration to the initial duration (120 min).

3. Trial Paused for Safety Concerns: Pegloticase 16 mg Q4 Wks does not appear to be well-tolerated based on the emerging AE profile. The trial would be paused for reevaluation.

The decision outcome for Cohort 1 and planned decision for Cohort 2 will be made by the internal Horizon team (input from a minimum of Medical Monitor and Pharmacovigilance Safety Physician).
If the decision outcome from the initial Cohort 1 analysis is to enroll additional subjects into Cohort 1, another Cohort 1 analysis will be performed to establish planned decision for Cohort 2.

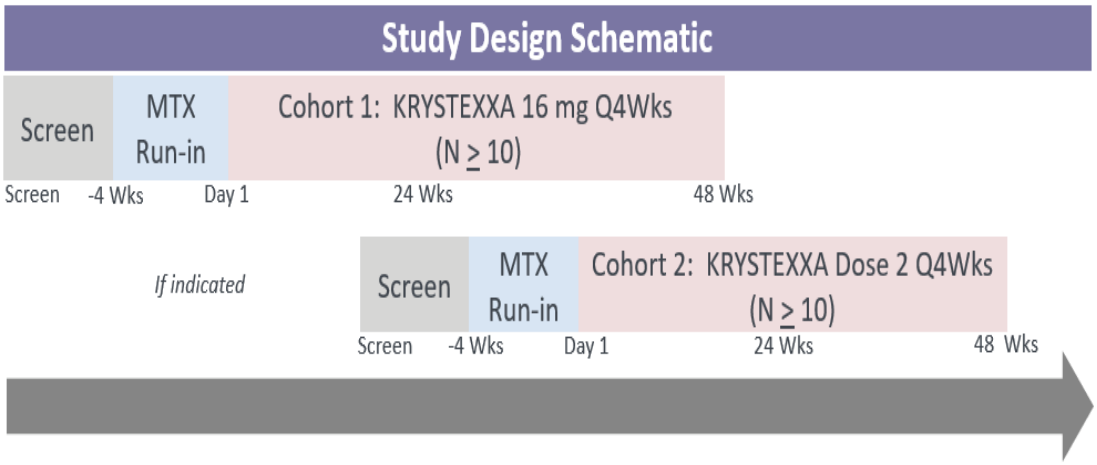
For this second cohort, during the Pegloticase + MTX Period, pegloticase will be administered intravenously (IV) every 4 weeks from Day 1 through the Week 20 Visit for a maximum of 6 infusions over the Week 24 treatment period (Day 1 and Weeks 4, 8, 12, 16, and 20), with an optional extension through the Week 48 visit for a total of up to 12 infusions (at Weeks 24, 28, 32, 36, 40, and 44).

All trial procedures for this cohort will be performed similarly to those for the first cohort (in the exception of the infusion duration, if applicable).

The Horizon trial team will review reported events of infusion reactions, MACE and anaphylaxis.

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

Figure 9.1 Schematic of Trial Design



9.2 Discussion of Trial Design

This is a Phase 4, open-label, multicenter, efficacy, safety, PK and PD trial of up to 2 dose levels of IV pegloticase infusions Q4 Wks, up to 6 IV infusions over 24 weeks (20 Wks + a 4 Wk End of Trial Visit), co-administered with weekly oral doses of MTX, to subjects with symptomatic chronic refractory gout. Subjects who may benefit from additional pegloticase treatment, may receive optional Q4 Wk dosing for an additional 6 infusions (Wk 24 through Wk 44 + a 4 Wk End of Trial Visit) for a total of 48 weeks. All subjects will be followed for approximately 4 weeks after their last infusion and after a minimum of 3 months after their last dose of MTX (for non-vasectomized male participants).

9.3 Selection of Trial Population

9.3.1 Inclusion Criteria

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

1. Willing and able to give informed consent.
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.
3. Adult men or women ≥18 and <80 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 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 as evidenced by either clinical synovitis on the clinical examination or the presence of typical gouty erosion(s) on hand and/or foot X-rays
5. Willing to discontinue any oral urate lowering therapy for at least 7 days prior to MTX dosing at Week -4 and remain off while receiving pegloticase treatments.
6. Women of childbearing potential (including those with an onset of menopause <2 years prior to screening, non-therapy-induced amenorrhea for <12 months prior to screening, or not surgically sterile [absence of ovaries and/or uterus]) must have negative serum/urine pregnancy tests during Screening and Week -4; subjects must agree to use 2 reliable forms of contraception during the trial, 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 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.

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 trial, beginning with the initiation of MTX at Week -4 and continuing and for at least 3 months after the last dose of MTX.
8. Able to tolerate MTX 15 mg orally for 4 weeks (Week -4 through Day 1) prior to enrollment.

9.3.2 Exclusion Criteria

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

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

coronary syndrome (myocardial infarction or unstable angina), or uncontrolled blood pressure (>160/100 mmHg) prior to enrollment at Day 1.

12. Pregnant, planning to become pregnant, breastfeeding, planning to impregnate female partner, or not on an effective form of birth control, as determined by the Investigator.
13. Prior treatment with pegloticase, another recombinant uricase (rasburicase), or concomitant therapy with a polyethylene glycol-conjugated drug.
14. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product.
15. Contraindication to MTX treatment or MTX treatment considered inappropriate.
16. Known intolerance to MTX.
17. Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to MTX administration at Week -4 or plans to take an investigational drug during the trial.
18. Liver transaminase levels (AST or ALT) > 1.25 X 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 <4000/µl, hematocrit <32 percent, or platelet count <75,000/µl.
21. Currently receiving systemic or radiologic treatment for ongoing cancer, excluding non-melanoma skin cancer.
22. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix.
23. Diagnosis of osteomyelitis.
24. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
25. Unsuitable candidate for the trial, 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 trial.
26. Alcohol use in excess of 3 alcoholic beverages per week.
27. A known intolerance to all protocol standard gout flare prophylaxis regimens (i.e. subject must be able to tolerate at least one: colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤10 mg/day).
28. Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest X-ray may be performed during Screening.

9.3.3 Removal of Subjects from Therapy or Trial

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

9.3.3.1 Removal of Subjects from Pegloticase Therapy

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

- Lost to Follow-up. The subject does not return to the clinic for scheduled assessments, and does not respond to the site's attempts to contact the subject.
- Lack of Efficacy. (i.e., sUA level >6 mg/dL at 2 consecutive visits beginning with the Week 1 Visit).
- Adverse Event. The subject experiences an AE that imposes an unacceptable risk to the subject's health (e.g., anaphylactic reaction), or the subject is unwilling to continue therapy because of an AE. Subjects who discontinue due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for the event is obtained.
- Physician Decision. The Investigator has determined that pegloticase administration poses an unacceptable risk to the subject or is otherwise contraindicated (specify reason).
- Withdrawal by Subject. Subject refusal of additional therapy or trial related procedures (specify reason).
- Trial Terminated by Sponsor. The Sponsor, IRB, or regulatory agency terminates the trial.
- Pregnancy
- Death

9.3.3.1.1 Trial considerations for subjects ending pegloticase infusions prior to 20 or 44 weeks

- Methotrexate, along with folic acid, will be discontinued at the time of cessation of pegloticase infusions.
- All subjects will complete the End of Pegloticase Infusions Visit and will remain on trial through Week 24 (or Week 48 for subjects who participate in the optional extension period) regardless of whether they stop infusions due to sUA stopping criteria or other reason (e.g. withdrawal of consent for pegloticase infusions). Subjects are encouraged to continue to participate in all visits through the end of the trial at Week 24 (or Week 48 for subjects who participate in the optional extension period). Subjects are especially encouraged to complete trial visits at the trial site during key efficacy and safety collections at Weeks 4, 12, 20, 24, 36, and 48 End of Trial/Early Termination, so that sUA labs and other key assessments can be completed.
- During visits between these key efficacy and safety collection visits, in subjects who have stopped infusions, subjects may complete trial visits in person or via telephone to collect AEs, concomitant medications and gout flare information.
- Activities related to pre/post infusion monitoring or medication dispensation will not be completed once a subject has stopped pegloticase infusions. These activities include:
    - MTX compliance/reconciliation
    - Infusion reaction prophylaxis

  - IR prophylaxis compliance
  - Folic acid compliance
  - Pegloticase infusion
  - Pegloticase PK sampling
  - [redacted]
  - MTX drug/dispensation related items
- Re-introduction of oral ULT's should not start until after the End of Pegloticase Visit laboratory tests are collected.

Post Treatment Follow-up:

AE/SAE follow-up will occur at the subject's scheduled visit approximately 4 weeks after the last pegloticase infusion or MTX dose. Those subjects that dose MTX and do not infuse pegloticase or ET from the trial for whom 4 weeks of safety follow up is not available will be contacted (Phone/Email) if subject agrees, to assess AE/SAEs approximately 4 weeks post MTX dose or 4 weeks post ET date. Assessments will include any AE/SAEs that have occurred within the last 4 weeks and will 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 4 weeks/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 inquiry will be conducted 3 months after MTX discontinuation regarding partner pregnancy (inquiry can occur during the 3-month Post Treatment Follow-up). Note: Subjects that agree to continue study visits post end of pegloticase visit will collect the 4 Wks post treatment follow up as part of the subjects continued visits. In the event a subject continues visits after the end of pegloticase but the visit is not at least 4 Wks post treatment then the safety follow-up phone call will still be required.

9.3.3.2 Removal of Subjects from Trial

In addition to completion of therapy and designated trial visits through Week 24 (or 48 for subjects who participate in the optional extension period), the reason for discontinuation from the trial should be recorded on the eCRF using 1 of the following categories:

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

9.3.4 Replacement Policy

9.3.4.1 Subjects

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

9.3.4.2 Centers

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

- Excessively slow recruitment.
- Poor protocol adherence.

9.3.4.3 Screen Failures

Subjects who do not meet all of the inclusion criteria or meet any of the exclusion criteria between Screening and Enrollment at Day 1 will be considered screen failures.. Screen failures may be allowed to rescreen, or retest laboratories for the study if both the Investigator and Sponsor are in agreement regarding rescreening/retesting and if the Investigator determines that they can satisfy all of the eligibility criteria.

9.4 Treatments

9.4.1 Treatments Administered

During the MTX 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 not be fasting on the day of infusions and will be encouraged to have a snack or normal meal before or after the infusion.

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 the date and time of each dose should be recorded in the dosing calendar. Since subjects will be required to dose MTX within 3 days of each infusion, the day of the week the subject is instructed to dose MTX should be taken into consideration.

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 Periods, MTX should be taken weekly until one week after the last infusion Week 21 or Week 45 for the extension portion. On weeks with infusions, MTX should be

taken 1 to 3 days prior to the pegloticase infusion. 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 Periods, if a subject becomes unable to tolerate the MTX the dosage may be decreased.

Subjects will also take folic acid 1 mg (with the option to increase to 2 mg daily at the discretion of the Investigator) orally every day beginning at Week -4 (the start of MTX) until the Week 21 Visit (Week 45 for the optional extension portion of the trial).

9.4.1.1 Folic Acid

Subjects will take folic acid 1 mg (or increase to 2 mg at the discretion of the Investigator) orally every day beginning at Week -4 (the start of MTX) until Week 21 or Week 45 Visit if the subject continues in the optional portion of the trial.

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

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

9.4.1.2 Gout Flare Prophylaxis

It is required that before a subject begins the pegloticase + 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 should continue flare prophylaxis throughout the pegloticase treatment per American College of Rheumatology guidelines [FitzGerald JD et al.2020].

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

9.4.1.3 Infusion Reaction Prophylaxis

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

If the subject is allergic to acetaminophen, then naproxen, salicylate, trisilicate, diclofenac or celecoxib may be used in substitution. If the subject is allergic to all of the above, the subject will not be allowed to participate in the study.

If the subject is allergic to fexofenadine, another antihistamine in a dose equivalent to 180 mg fexofenadine may be used in substitution after consultation with the sponsor's medical monitor. It the subject is allergic to all antihistamines, the subject will not be allowed to participate in the study.

Substitution of the corticosteroid is not allowed.

Please note, the alternatives list provided above is non-exhaustive and any substitutions must be approved by the Medical Monitor.

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

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

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

9.4.2 Identity of Investigational Products

9.4.2.1 Pegloticase

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

9.4.2.2 Methotrexate

MTX 2.5 mg tablets for oral administration during the Run-In Period (Week -4 through Day 1) and the Pegloticase + MTX Period (Day 1 through Week 21 or Week 45) will be provided to subjects as a commercially available generic.

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 for MTX administration. Since subjects will be required to dose MTX within 1-3 days of each infusion, the day of the week the subject is instructed to dose MTX should be taken into consideration.

Subjects previously taking MTX may be allowed to enroll in the trial upon consultation and approval to proceed from the Sponsor. The subject must be willing to discontinue MTX for at least 4 weeks prior to trial-specific MTX dosing at Week -4 and be able to have MTX dosing adjusted, as required per the protocol.

See MTX Full Prescribing Information for additional detail.

9.4.3 Labeling

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

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

9.4.4 Storage

Before preparation for use, pegloticase will be stored in the carton, maintained under refrigeration between 2ºC and 8ºC (36ºF and 46ºF), protected from light, and will not be shaken or frozen. Pegloticase diluted in infusion bags is stable for 4 hours at 2°C to 8°C (36°F to 46°F) and for 4 hours at room temperature (20°C to 25°C, 68°F to 77°F).

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

9.4.5 Drug Accountability

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

Subjects will bring the MTX dosing calendar to each trial 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 tablets and re-dispense the bottle to the subject. At the end of the trial or if the subject prematurely discontinues the trial, the subjects will return any unused or partially used trial drugs to the site.

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

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

9.4.6 Trial Drug Administration and Timing of Dose for each Subject

9.4.6.1 Description of Clinical Supplies

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

9.4.6.2 Determination of Dose Volume

Pegloticase will be administered as an admixture of 16 mg (two 8 mg vials), or, if a higher dose is selected, it will be administered as an admixture of required number of 8 mg vials in 50mL to 250 mL of 0.45% to 0.9% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion (see IP Manual for details).

In the event of an IR, the infusion should be slowed, or stopped, and restarted at a slower rate at the discretion of the Investigator. Infusions subsequent to an IR in an individual subject may be given in a larger volume of diluent, not to exceed 500 ml. In this case, the infusion duration can also be extended at the Investigator's discretion following an IR. The dose volume and/or duration may be adjusted, as necessary, upon determination from the internal team and/or Safety Review Team.

9.4.6.3 Details Concerning Timing and Dose Administration

9.4.6.3.1 Preparation and Administration

9.4.6.3.1.1 Preparation

Vials of pegloticase will be visually inspected for particulate matter and discoloration before administration, whenever solution and container permit. Vials will not be used if either is present. Using appropriate aseptic technique, 1 mL of pegloticase will be withdrawn from each vial into a sterile syringe. Aliquots from each of the vials used will be withdrawn for dose preparation. Any unused portion of product remaining in the vials will be discarded. Syringe contents will be injected into a single 250 mL or 50 mL (depending on the cohort dose/volume) bag of 0.9% or 0.45% Sodium Chloride Infusion, USP for IV infusion and will not be mixed or diluted with other drugs. The infusion bag containing the dilute pegloticase solution will be inverted a number of times to ensure thorough mixing but will not be shaken. In accordance with good pharmacy practice, gloves will be worn during preparation of the dose.

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

9.4.6.3.1.2 Dose and Administration

Methotrexate

During the MTX Run-in Period (Week -4 visit to Day 1), all subjects will take MTX 15 mg orally weekly.

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 stopping criteria; however, if a subject does not do so, MTX must be taken ≥60 minutes prior to each pegloticase infusion. Investigators may choose to have subjects take the weekly dose divided over the day (i.e. BID, TID). The total MTX dose should be taken within 24 hours, preferably the same calendar day each week, with the date and time of each dose recorded in the dosing calendar. If a subject becomes unable to tolerate the MTX during the Pegloticase + MTX Period, the dosage may be decreased.

Refer to Section 9.4.12 for contraception requirements.

Subjects will take folic acid 1 mg (2 mg at the Investigators discretion) orally every day beginning at Week -4 (the start of MTX) until 1 week after the last infusion at Week 21 (or if subject continues into the optional portion of the trial, then Week 45 Visit).

Pegloticase

Pegloticase (KRYSTEXXA®) is commercially available in the United States and will be packaged in sterile, single-use 2-mL glass vials with a Teflon®-coated (latex-free) rubber infusion stopper to deliver pegloticase as 8 mg of uricase protein in 1 mL volume. For the first, 16 mg cohort, pegloticase will be administered as an admixture of 16 mg (from two 8 mg vials) in 250 mL of 0.45% or 0.9% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump. Pegloticase will not be administered as an IV push or bolus.

If the second cohort will receive a higher dose of pegloticase (between 24 and 32 mg), it will be administered as an admixture by injecting required number of 8 mg vials into 50 to 250 mL of 0.45% to 0.9% Sodium Chloride Infusion, United States Pharmacopeia (USP) for IV infusion by gravity feed or infusion pump (see IP manual for details).

Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase infusion (see Section 9.5.1.1).

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

In a patent IV site, using tubing with no in-line filter, the pegloticase preparation will be infused over approximately 120±15 minutes or 60±15 minutes while the subject is under close observation for any signs of distress. If an in-line filter is used, it should be 0.2 µm or larger. At the end of the infusion, the IV line will be flushed with 10 mL of normal saline to ensure the full dose is administered. The date and time of infusion start and stop and the start and stop time of the IV flush will be recorded.

9.4.6.3.2 Dose Modifications, Interruptions, and Delays

9.4.6.3.2.1 Pegloticase Modifications

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

Infusions subsequent to an IR in an individual subject may be given in a larger volume of diluent, not to exceed 500 mL. In this case, the infusion duration can also be extended at the Investigator's discretion following an IR. The total volume and duration of infusion will be captured in the medical record and eCRF.

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

9.4.6.3.2.2 MTX Dose Titration Algorithm and Intolerance Criteria

During the MTX Run-In Period subjects will be considered a screen failure if any of the following new laboratory findings or symptoms reflecting MTX intolerance occur (the subjects may be allowed to retest to confirm eligibility prior to enrollment):

1. Abnormal Hematology findings:
    a. WBC < 3.5 x 10^9/L
    b. Platelets < 75 x 10^9/L
    c. Hematocrit < 32%
2. Abnormal hepatic function findings:
    a. AST/ALT >1.5 x upper limit of reference range and
    b. Albumin < lower limit of reference range
3. Abnormal renal function: eGFR <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 repeat laboratory tests may be needed to confirm these new findings. In addition, if minor clinical symptoms emerge, such as mild stomatitis, mild GI discomfort, etc., the investigator may

increase folic acid dose (e.g. 2 mg daily) or recommend a divided dose of MTX (e.g. 3 tabs of 2.5 mg in the morning and evening on the day of dosing); if symptoms improve, the subject will not be considered a screen failure on the basis of that symptom.

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 predispose to new or worsening infection (e.g. undergoing surgery, hospitalization, being treated with antibiotics, having a clinical infection, developing new clinically significant pericardial / pleural effusion or ascites)

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

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

1. ALT/AST > 1.5 x ULN on 3 of any 5 consecutive measures

2. Albumin < 0.8 x LLN on 2 consecutive measures
3. Any laboratory or clinical symptoms leading to temporary stop on 3 consecutive measures, in which case the medical monitor will review to consider re-initiation, a continued temporary stop, or a permanent stop in discussion with the PI.

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

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

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

9.4.6.3.2.3 Gout Flare Treatment

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

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

9.4.6.3.2.4 Infusion Reaction Treatment

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

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

- A physical examination will be performed to capture medically relevant details, including, but not limited to, a thorough dermatologic examination for detection of erythema, urticaria (hives), or peri-oral or lingual edema; a chest examination for breath sounds, stridor or wheezing; and a cardiac examination with attention to irregular heartbeat.

- Vital signs (sitting or supine blood pressure, heart rate, respiratory rate, and body temperature) will be captured at least every 30 minutes until the resolution or stabilization of the AE.
- A serum sample will be collected in a serum-separating tube at the time of the event or at the subsequent visit. The sample will be centrifuged, frozen at -20°C or colder, and stored for the batch shipment to a Horizon designated laboratory for evaluation of pegloticase antibodies at a future date.
- When possible, a 12-lead ECG will also be performed at the time of infusion reaction.

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

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

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

9.4.7 Method of Assigning Subjects to Treatment Groups

Subjects who are eligible and complete the Run-In period will be consecutively assigned to cohort 1 followed by cohort 2, if required.

Once the observations for the first two 4-week periods (Week 4 and Week 8) have been obtained from approximately the first 10 subjects in the first cohort, the data may be analyzed to determine if 1) 5 more subjects in the first cohort should be enrolled, 2) > 5 subjects should be enrolled in the first cohort, 3) enrollment in the first cohort should discontinue, and/or 4) enrollment for a second cohort should begin. This determination will be made based on assessment of the available 4- and 8-week pharmacokinetic, pharmacodynamic, efficacy, safety and tolerability data from the approximately first 10 subjects in the first cohort.

9.4.8 Blinding

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

9.4.9 Prior and Concomitant Therapy

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

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

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

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

9.4.10 Restricted Medications

Subjects should not receive the following medications for at least 7 days prior to MTX dosing at Week-4 and remain off when receiving pegloticase infusions:

- Oral urate-lowering therapies including allopurinol, febuxostat, probenecid, lesinurad, or other ULT for gout. Re-introduction of oral ULT's should not start until after the End of Pegloticase Visit (or End of Trial) laboratory tests are collected.

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

- Any PEG-conjugated drug
- Any other investigational agent
- Any methotrexate other than the trial approved investigational product, azathioprine, mycophenolate mofetil, or other systemic immunosuppressants aside from glucocorticoids for gout flare prophylaxis (≤ 10 mg prednisone or equivalent per day) or intermittent gout flare treatment
- If a subject is treated with antibiotics, refer to Section 9.4.6.3.2.2.

9.4.11 Treatment Compliance

A dosing calendar will be provided to subjects at the Week -4 Visit for recording the dose/s of MTX and the date and time of each dose on each calendar day of MTX administration. The dosing calendar and bottle of MTX should be brought to each trial visit for assessment of compliance. Adherence to the MTX regimen will also be recorded by the trial coordinator at trial visits in the

eCRF by recording the date of each MTX dose (mg), frequency and time of each dose per calendar day. Subjects who have taken at least 80% of the protocol specified amount of MTX will be considered compliant. Noncompliant subjects will be re-educated on compliance.

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

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

9.4.12 Contraception Requirements

Women of childbearing potential (including those with an onset of menopause <2 years prior to screening, non-therapy-induced amenorrhea for <12 months prior to screening, or not surgically sterile [absence of ovaries and/or uterus]) must agree to use 2 reliable forms of contraception during the trial, 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 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 their female partner during the trial and for at least 3 months after the last dose of MTX. Men must agree to use appropriate contraception from Week -4 through 3 months post the last dose of MTX. Appropriate contraception methods include condom use and abstinence.

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

The Schedule of Assessments is provided in Section 2.1.

9.5.1 Efficacy Variables

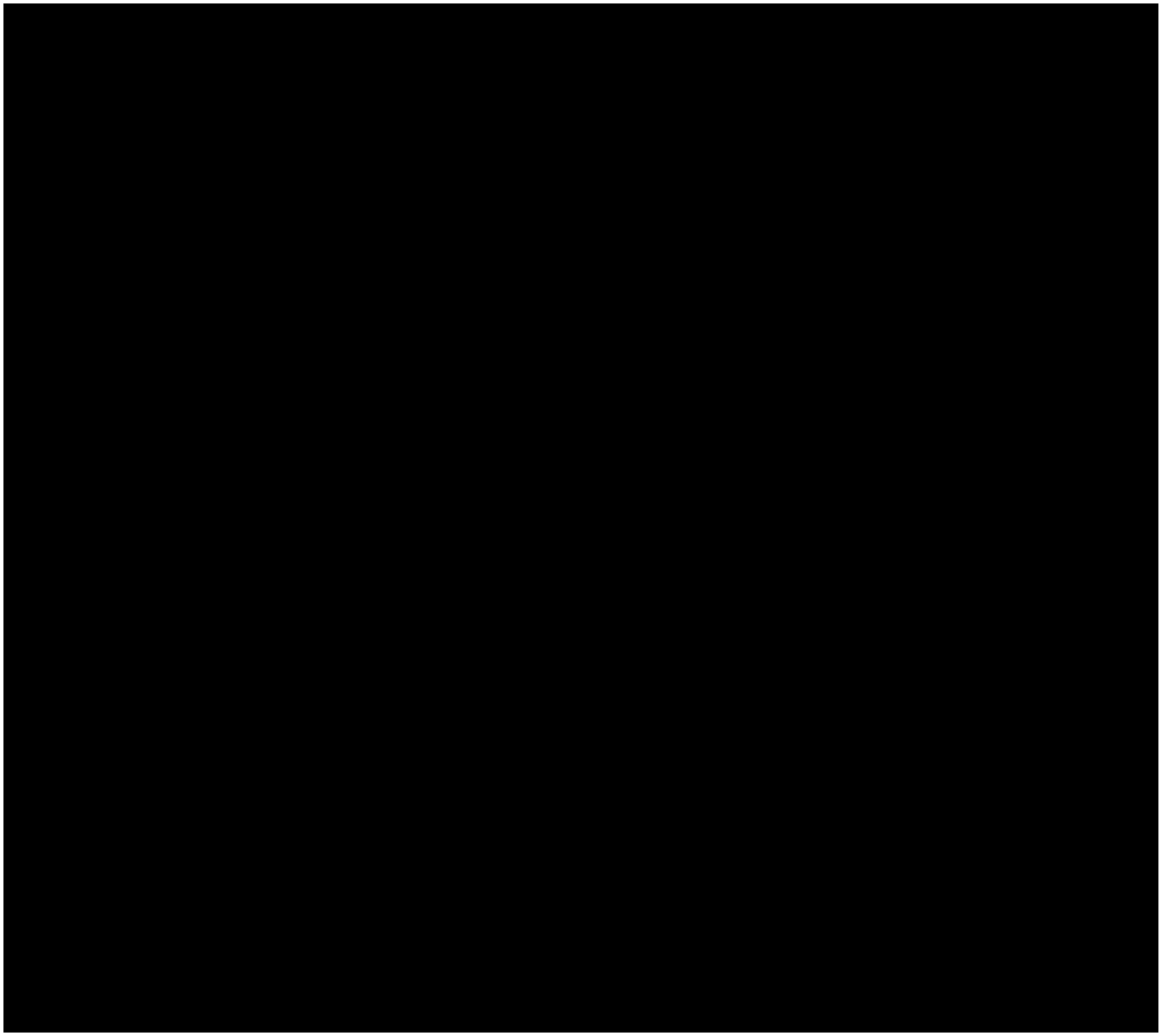
Efficacy will be assessed based on measurement of sUA levels, [redacted]

9.5.1.1 Serum Uric Acid

Serum samples for measurement of sUA levels will be collected at the Screening Visit, the Week -4 Visit (prior to the first dose of MTX), and the Week -2 Visit during the Run-in Period. On Day 1, and at the Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and Week 24/End of Trial/Early Termination Visit; as well as 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, and Week 48/End of Trial/Early Termination Visit for subjects that participate in the optional treatment extension. On infusion visit dates a pre-dose and post dose sUA will be collected to be shipped to the Central laboratory. See the Laboratory Manual for instructions.

In the event of an AE suspected to be an infusion reaction, a serum sample will be collected at that time or at the subsequent visit for evaluation of pegloticase antibodies. If for any reason the week prior to each infusion, central laboratory sUA data is not received or compromised, a local laboratory sample will need to be resulted prior to the infusion to be certain the subject has not met the stopping criteria.

A subject with an sUA level >6 mg/dL (based on the local or central laboratory) at 2 consecutive trial visits, beginning with the Week 1 Visit, (not including post-infusion samples) will discontinue pegloticase + MTX treatment and remain in the trial.



[redacted]

9.5.3 Pharmacokinetic and Anti-drug Antibody Measurements

Serum samples for PK analysis will be collected after the end of infusion on Day 1 (prior to discharge); at Week 1, Week 2, Week 3, prior to the pegloticase infusion and after the end of infusion (prior to discharge) at the Weeks 4; at Week 6 and Week 7, prior to the pegloticase infusion and post the infusion at Weeks 8 and 16, at Week 22 and prior to and post the pegloticase infusion at Week 24 (unless the subject is not entering the optional Section 2 then no post-infusion sample is required for subjects at Week 24), and prior to and post the pegloticase infusion at Week 36. Additional PK samples will be collected at non-infusion visits: End of Pegloticase visit and Week 48/End of Trial/Early Termination visit.

Serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 2, 4, 8, 16, 24, 36; and at the non-infusion End of Pegloticase Infusions visit (if applicable) or the Week 48/End of Trial/Early Termination visit.

Blood samples will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 4, 12, 24 and 36 Visits during the Pegloticase + MTX Period for [redacted] analysis.

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

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

9.5.3.1 Additional Sample Collection for Future Use

Optional urine and blood samples will be collected from each consenting subject prior to the first dose of MTX at Week -4 visit, prior to the infusion at Day 1 and Weeks 12, 24, 36 and the End of Pegloticase Infusions Visit (if applicable) and the Week 48/End of Trial/Early Termination.

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

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

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

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

9.5.4 Safety Variables

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

9.5.4.1 Adverse Events

9.5.4.1.1 Definitions

9.5.4.1.1.1 Adverse Event Definition

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

Examples of an AE include:

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

Issues that will not be considered an AE include:

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

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

9.5.4.1.1.2 Serious Adverse Event Definition

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

- Results in death
- Is life threatening
  NOTE: The term 'life threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe, prolonged, or untreated.
- Requires hospitalization or prolongation of existing hospitalization
  NOTE: Hospitalization signifies that the subject has been admitted to the hospital as an inpatient for any length of time. Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of SAEs and not resulting in hospital admission does not qualify for this category, but may be appropriately included in category g (see below). Complications that occur during hospitalization are usually AEs. If a complication prolongs hospitalization or fulfills any other serious criterion, the event will be considered as serious. When in doubt as to whether 'hospitalization' occurred, consult the Sponsor's Medical Monitor.
  Hospitalization will not be considered an AE in and of itself. It will be considered an outcome of an AE. Therefore, if there is no associated AE, there is no SAE. For example, hospitalization for elective or pre-planned treatment of a pre-existing condition that did not worsen from baseline will not be considered an AE.
- Results in persistent or significant disability/incapacity
  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may temporarily interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether expedited reporting as serious is appropriate in other situations; specifically, important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These should usually be considered serious. Examples of such events are invasive cancers, intensive treatment in an emergency room or

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

9.5.4.1.1.3 Non-Serious Adverse Event Definition

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

9.5.4.1.1.4 Unexpected Adverse Event Definition

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

9.5.4.1.1.5 Adverse Events of Special Interest

AEs of special interest include IRs, anaphylaxis, gout flares, and MACE including type I and type II non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure. The Horizon trial team will evaluate the AESIs of IR, anaphylaxis and cardiovascular events.

Infusion Reaction

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

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

Anaphylaxis

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

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

Gout Flares

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

Cardiovascular Events

Cardiovascular adverse events will be collected as part of the AE collection. The Horizon trial team will evaluate major adverse cardiovascular events (MACE). MACE will include type I and type II non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure.

9.5.4.1.2 Documentation of Adverse Events

AE monitoring will begin from the signature of the ICF until the Safety Follow-up Visit.

SAE monitoring will begin from the signature of the ICF until the Safety Follow-up Visit.

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

9.5.4.1.3 Intensity of Adverse Events

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

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

9.5.4.1.4 Relationship to Trial Drug

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

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

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

9.5.4.1.5 Reporting and Documenting SAEs and Product Complaints

9.5.4.1.5.1 Serious Adverse Events

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

9.5.4.1.5.2 Product Complaints

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

9.5.4.1.6 Follow-up of Adverse Events

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

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

9.5.4.1.7 Medication Error and Overdose

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

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

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

9.5.4.1.8 Review of Adverse Events and Emerging New Safety Information

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

9.5.4.1.9 Reporting of IND Safety Reports

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

9.5.4.1.10 Development Safety Update Reports

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

9.5.4.2 Pregnancy Reporting

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

Information must be obtained and reported if a female subject suspects that she has become pregnant during the trial (including the MTX Run-in Periods) up to 30 days after the last dose of trial treatment, or if a female partner of male subject suspects that she has become pregnant during the trial (including the MTX Run-in Periods) up to 3 months (approximately 90 days) after their male subject partner discontinues MTX. The Investigator will instruct the female subject to stop taking all trial drugs. A serum pregnancy test should be performed if any female subject or female partner of a male subject suspects that she has become pregnant during the time frame as defined above. If pregnancy is confirmed, female subject will be removed from pegloticase therapy and should remain on trial barring withdrawal of consent for trial participation. Pregnancy will be followed up until the outcome of pregnancy. The Investigator should report pregnancies to the Sponsor by submitting the completed pregnancy report form by email to clinicalsafety@horizontherapeutics.com or via fax within 24 hours after becoming aware that the patient/patient's female partner has become pregnant.

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

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

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

9.5.4.3 Medical History

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

9.5.4.4 Vital Signs, Height, and Weight

Routine vital signs, including blood pressure, respiratory rate, temperature, and heart rate will be measured at Screening, Week -4, Day 1 and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and the End of Pegloticase Infusions Visit (if applicable), Week 48/End of Trial/Early Termination Visit. Heart rate and blood pressure measurements should be taken after the subject has been in a sitting position and in a rested and calm state with proper positioning including back support, feet flat on the floor, for at least 5 minutes. Subjects arm should be supported at heart level; and cuff placed on the bare arm. A large cuff should be used as needed to fit the upper arm and a consistent arm is to be used at each trial visit. The Korotkoff phase V will be used to determine diastolic blood pressure. During the Pegloticase + MTX Period trial 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, 24, 36 and at the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 48/End of Trial/Early Termination.

Height will be collected at the Screening Visit only.

Vital sign monitoring during IR is described in Section 9.4.6.3.2.4.

9.5.4.5 Physical Examinations

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

A targeted physical examination per investigator judgement will be conducted at Week -4, Day 1, and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20, 24, 36 and the non-infusion End of Pegloticase Infusions Visit (if applicable), and Week 48/End of Trial/Early Termination; at a minimum this should include heart, lungs, and abdominal exam.

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

9.5.4.6 Electrocardiogram

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

When possible, a 12-lead ECG will also be performed at the time the AESI (See Section 9.5.4.1.1.5) of infusion reaction, anaphylaxis and MACE is suspected.

9.5.4.7 Clinical Laboratory Safety Tests

Blood (for hematology and clinical chemistry) will be collected at the Screening, Week -4 (prior to the first dose of MTX), and Week -2 Visits during the Run-in Period; prior to pegloticase infusion on Day 1 and at the Weeks 2, 4, 8, 12,16, 20, 24, 36 and within 2 weeks following final infusion if prior to Week 44 (if applicable), Week 48/End of Trial/Early Termination Visits. In addition blood will be collected for hs-CRP at Screening, Day 1, Weeks 12, 24, 36, End of Pegloticase Visit and Week 48/End of Trial/Early Termination Visit.

Urine (for albumin:creatinine ratio) samples will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 12, 24, 36 and the non-infusion End of Pegloticase Infusions Visit (if applicable) and Week 48/End of Trial/Early Termination Visits.

For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit. A urine pregnancy test will be performed prior to each infusion and approximately 4 weeks after the last pegloticase infusion or MTX (whichever is the later) dose if the subject has not ovulated; at the End of Pegloticase Infusions Visit (if applicable), the Week 48/End of Trial/Early Termination Visit.

Safety laboratory assessments will include:

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

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

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

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

9.5.4.8 Assessment of Gout Flare

There is no validated instrument to assess gout flares. Gout flares will be assessed at the time points specified in Section 2.1. Investigators will assess gout flares based on subject self-reporting, with investigator confirmation of flare based on subject questioning and/or direct observation. All gout flares will be recorded as adverse events with the required AE reporting information. Investigators will also ask the subject a series of questions related to each gout flare,

to document subject report of swollen joints, joints that are warm to touch, and level of joint pain [Gaffo et al, 2012].

9.5.5 Appropriateness of Measurements

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

9.5.6 Trial Procedures

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

9.5.6.1 Screening/MTX Run-in Period

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

9.5.6.1.1 Screening Visit (Within 35 Days Prior to the First Dose of MTX at Week -4)

- Obtain signed, written informed consent. Refusal to provide this permission excludes an individual from eligibility for trial participation. Record date informed consent was given and who conducted the process on the appropriate source documentation.
- Determine trial eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Obtain demographic information.
- Investigator review of clinical status and subject treatment goals.
- Collect complete gout history (on gout-specific CRF), other relevant medical/surgical history, and medication history, including gout medications starting at the time of diagnosis and up to screening (on gout medications-specific CRF), substance use history, and all other medications currently being taken at screening (see Section 9.4.10 for restrictions regarding medications).
- Chest X-ray for subjects that do not have a chest X-ray within 2 years prior to Screening if deemed necessary by the Investigator. Subjects that do not have a hand/foot X-ray prior to Screening may have an X-ray done during Screening to confirm Inclusion Criterion 4, if deemed necessary by the Investigator.

- Perform a complete physical examination, including assessment of HEENT, heart, lungs, abdomen, skin, extremities, neurological status and musculoskeletal including an assessment for the presence of tophi.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate), (see Section 9.5.4.4).
- Record height.
- Record weight.
- Perform 12-lead ECG.
- Obtain blood samples for hematology, clinical chemistry analysis, hs-CRP.
- Obtain a serum sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples to evaluate sUA (only 1 sample for central laboratory)
- Obtain blood sample for G6PD (central laboratory or locally).
- Administer [redacted]
- Record [redacted]
- Inquire about AEs and concomitant medication use.

9.5.6.1.2 Week -4 (MTX Run-in Period)

- Confirm trial eligibility through review of the inclusion/exclusion criteria and MTX tolerability (see Section 9.3).
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) (see Section 9.5.4.4).
- Record weight.
- Document gout flares and intensity.
- Administer [redacted]

- Record [redacted]
- [redacted]
- Obtain blood samples for hematology and clinical chemistry analysis.
- Obtain a blood sample for measurement of sUA (only 1 sample for central laboratory).
- Obtain optional urine and whole blood and serum samples from subjects who consent for future analysis.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Provide dosing calendar for subjects to record the date and time they take MTX. (Additional calendar pages may be provided at future visits as needed).
- Dispense MTX via EDC and instruct site on what day of the week to dose MTX such that MTX will be taken 1-3 days of the infusions.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Remind subjects to dose 1 mg (or 2 mg at the Investigators discretion) folic acid daily
- Inquire about AEs and concomitant medication use.
- Subjects that take MTX starting at Week -4 and who are females of childbearing potential, will receive a safety follow-up phone call/e-mail approximately 4 Wks/30 days after the last dose of MTX in the trial to verify at least one ovulatory cycle has occurred since the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. Subjects who are non-vasectomized males, an inquiry will be conducted approximately 3 months after MTX discontinuation regarding partner pregnancy.

9.5.6.1.3 Week -2 (Run-in Period)

- Confirm trial eligibility through review of the inclusion/exclusion criteria and MTX tolerability (see Section 9.3).
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain a blood sample for measurement of sUA (only 1 sample for central laboratory).

- Obtain blood samples for hematology and clinical chemistry analysis.
- Assess MTX compliance by checking subjects' calendar vs. bottle pill count.
- Re-dispense MTX after compliance check.
- Ask Yes/No question regarding folic acid and gout flare prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Inquire about AEs and concomitant medication use.
- Subjects that take MTX during Run-In, and who are females of childbearing potential, will receive a safety follow-up phone call/e-mail approximately 4 Wks/30 days after the last dose of MTX in the trial to verify at least one ovulatory cycle has occurred since the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. Subjects who are non-vasectomized males, an inquiry will be conducted approximately 3 months after MTX discontinuation regarding partner pregnancy.
- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Day 1 visit.

9.5.6.2 Pegloticase + MTX Period

9.5.6.2.1 Day 1

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

Prior to Infusion

- Confirm trial eligibility through review of the inclusion/exclusion criteria and MTX tolerability (see Section 9.3). Subject is enrolled if eligibility and MTX tolerability are confirmed.
- Subject Enrollment
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion (See Section 9.5.4.4).
- Record weight.
- Administer [redacted].

- Record [redacted].
- [redacted]
- Document gout flares and intensity.
- Obtain a urine sample for albumin:creatinine ratio.
- Obtain blood samples for hematology, clinical chemistry analysis, hs-CRP.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain 1 blood sample for measurement of sUA prior to the pegloticase infusion for shipment to the Central Laboratory.
- Obtain blood samples for [redacted] analysis prior to the infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Obtain optional urine and whole blood and serum samples from subjects who consent for future analysis.
- Assess MTX compliance by checking subjects' calendar vs. bottle pill count.
- Re-dispense or dispense additional MTX through EDC if needed.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- If the subject has not taken MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer the first dose of pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post Infusion

- Obtain blood samples for pegloticase PK analysis any time after the end of the infusion, prior to discharge from the site.
- Obtain 1 blood sample for measurement of sUA after the end of the pegloticase infusion for shipment to the Central Laboratory.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Inquire about AEs and concomitant medication use.

9.5.6.2.2 Week 1, Week 2, Week 3

- Assess MTX compliance and re-dispense or dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA.
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit (not including post-infusion samples) will discontinue treatment and remain in the trial.
- Obtain blood samples for pegloticase PK analysis.
- Week 2 only: Obtain a blood sample for hematology and chemistry.
- Week 2 only: Obtain blood samples for anti-PEG and anti-uricase IgG antibodies.
- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.
- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 4 infusion visit.

9.5.6.2.3 Week 4

Prior to the Infusion

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)
- Obtain a pre-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

- If the subject has not taken MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Assess MTX compliance vs the calendar and re-dispense or dispense MTX.
- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion (See Section 9.5.4.4).
- Administer [redacted].
- Record [redacted].
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology, clinical chemistry analysis.
- Obtain blood samples for pegloticase PK analysis prior to the infusion.
- Obtain blood samples for [redacted] analysis prior to the infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush

Post Infusion

- Obtain a post-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
- Obtain blood samples for pegloticase PK analysis any time after the end of the infusion, prior to discharge from the site.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Inquire about AEs and concomitant medication use.

9.5.6.2.4 Week 5

- Assess MTX compliance and re-dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA.
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.

9.5.6.2.5 Week 6 and Week 7

- Assess MTX compliance and re-dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA.
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- Obtain blood samples for pegloticase PK analysis.
- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.
- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 8 infusion visit.

9.5.6.2.6 Week 8

Prior to the Infusion

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)

- Obtain a pre-infusion sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).

    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

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

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

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion. (See Section 9.5.4.4).

- Record weight.

- Assess MTX compliance and re-dispense MTX.

- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.

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

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

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

- Obtain blood samples for hematology, clinical chemistry analysis.

- Obtain blood samples for pegloticase PK analysis.

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

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

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post Infusion

- Obtain a post-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).

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

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

- Inquire about AEs and concomitant medication use.

9.5.6.2.7 Week 9, Week 10, Week 11

- Assess MTX compliance and re-dispense MTX.

    - Obtain a blood sample (1 sample) for measurement of sUA. Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.

- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 12 infusion visit.

9.5.6.2.8 Week 12

Prior to the Infusion

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)

- Obtain a pre-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).

    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

- If the subject has not taken MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- [redacted]
- Document gout flares and intensity.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion (See Section 9.5.4.4).
- Administer [redacted]
- Record [redacted].
- Assess MTX compliance and re-dispense MTX.
- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain blood samples for hematology, clinical chemistry analysis, hs-CRP.
- Obtain blood samples for [redacted] analysis prior to the infusion.
- Obtain a urine sample for albumin:creatinine ratio.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain optional urine and whole blood and serum samples from subjects who consent for future analysis.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post Infusion

- Obtain post-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).

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

- Inquire about AEs and concomitant medication use.

9.5.6.2.9 Week 13, Week 14, Week 15

- Assess MTX compliance and re-dispense MTX.

- Obtain a blood sample (1 sample) for measurement of sUA.

    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.

- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 16 infusion visit.

9.5.6.2.10 Week 16

Prior to the Infusion

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)

- Obtain a pre-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).

    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

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

- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion (See Section 9.5.4.4).
- Assess MTX compliance and re-dispense MTX.
- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology, clinical chemistry analysis.
- Obtain blood sample for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Obtain blood samples for pegloticase PK analysis.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post Infusion

- Obtain a post-dose blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
- Obtain blood samples for pegloticase PK analysis any time after the end of the infusion, prior to discharge from the site.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).

- Inquire about AEs and concomitant medication use.

9.5.6.2.11 Week 17, Week 18, Week 19

- Assess MTX compliance and re-dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA.
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.
- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 20 infusion visit.

9.5.6.2.12 Week 20

Prior to the infusion

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)
- Obtain a pre-infusion sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- If the subject has not taken MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion. (See Section 9.5.4.4).
- Administer [redacted]
- Record [redacted].

- Assess MTX compliance and re-dispense MTX.
- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology and clinical chemistry analysis.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post infusion

- Obtain a post-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Inquire about AEs and concomitant medication use.

9.5.6.2.13 Week 21

- Assess MTX compliance and re-dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA.
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- Inquire about AEs and concomitant medication use.

9.5.6.2.14 Week 22

- Assess MTX compliance and re-dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA.
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial. nfusions if the both the Investigator and the Sponsor's medical monitor agree.
- Obtain blood samples for pegloticase PK analysis.
- Inquire about AEs and concomitant medication use.

9.5.6.2.15 Week 23

- Assess MTX compliance and re-dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA.
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.
- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 24 infusion visit if subjects will continue in the optional visits Weeks 24 through Week 48.

9.5.6.2.16 Week 24

Prior to Infusion (go to section 9.5.6.4 for subjects who are not continuing in the optional Weeks 24-48)

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)
- Obtain a pre-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

- If the subject has not taken MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- [redacted]
- Administer [redacted]
- [redacted].
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion. (See Section 9.5.4.4).
- Record weight.
- Obtain blood samples for hematology, clinical chemistry analysis, hs-CRP.
- Obtain blood samples for pegloticase PK analysis prior to the infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Obtain blood samples for [redacted] analysis prior to the infusion.
- Obtain optional urine and whole blood and serum samples from subjects who consent for future analysis.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain a urine sample for albumin:creatinine ratio.
- Assess MTX compliance and re-dispense MTX.
- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.

- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Investigator review of clinical status and subject treatment goals.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post Infusion

- Obtain a post-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
- Obtain blood samples for pegloticase PK analysis any time after the end of the infusion, prior to discharge from the site.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Inquire about AEs and concomitant medication use.

9.5.6.2.17 Week 26

- Assess MTX compliance and re-dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.
- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 28 infusion visit.

9.5.6.2.18 Week 28

Prior to the Infusion

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)

- Obtain a pre-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- If the subject has not taken MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion. (See Section 9.5.4.4).
- Assess MTX compliance and re-dispense MTX.
- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post Infusion

- Obtain a post-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Inquire about AEs and concomitant medication use.

- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 4 infusion visit.

9.5.6.2.19 Week 30

- Assess MTX compliance and re-dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.
- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 32 infusion visit.

9.5.6.2.20 Week 32

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)
- Obtain a pre-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- If the subject has not taken MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion. (See Section 9.5.4.4).
- Assess MTX compliance and re-dispense MTX.
- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.

- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post Infusion

- Obtain a post-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Inquire about AEs and concomitant medication use.
- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 4 infusion visit.

9.5.6.2.21 Week 34

- Assess MTX compliance and re-dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.
- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 36 infusion visit.

9.5.6.2.22 Week 36

Prior to the Infusion

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)
- Obtain a pre-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.
- If the subject has not taken MTX within the previous 1 to 3 days, administer MTX ≥60 minutes prior to pegloticase infusion.
- Document gout flares and intensity.
- Administer [redacted].
- [redacted].
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion (See Section 9.5.4.4).
- Record weight.
- [redacted]
- Assess MTX compliance and re-dispense MTX.
- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.

- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology, clinical chemistry analysis, hs-CRP.
- Obtain a urine sample for albumin:creatinine ratio.
- Obtain blood samples for pegloticase PK analysis prior to the pegloticase infusion.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies prior to the infusion.
- Obtain blood samples for [redacted] analysis prior to the infusion.
- Obtain optional urine and whole blood and serum samples from subjects who consent for future analysis.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post infusion

- Obtain a post infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
- Obtain blood samples for pegloticase PK analysis after the pegloticase infusion.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Inquire about AEs and concomitant medication use.
- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 4 infusion visit.

9.5.6.2.23 Week 38

- Assess MTX compliance and re-dispense MTX.
- Obtain a blood sample (1 sample) for measurement of sUA
    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.

- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 40 infusion visit.

9.5.6.2.24 Week 40

Prior to the Infusion

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)

- Obtain a pre-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).

    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

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

- Document gout flares and intensity.

- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion (See Section 9.5.4.4).

- Assess MTX compliance and re-dispense MTX.

- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.

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

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

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

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

- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post infusion

- Obtain a post-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).

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

- Inquire about AEs and concomitant medication use.

9.5.6.2.25 Week 42

- Assess MTX compliance and re-dispense MTX.

- Obtain a blood sample (1 sample) for measurement of sUA

    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.

- Subjects should be contacted by phone or e-mail to remind them to dose the 180 mg oral fexofenadine the day prior to Week 44 infusion visit.

9.5.6.2.26 Week 44

Prior to the Infusion

- Within 48 hours of the infusion obtain a local laboratory serum uric acid, if necessary (see Footnote 18 in Schedule of Assessments)

- Obtain a pre-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).

    - Stopping criteria: Subjects with an sUA level >6 mg/dL at 2 consecutive trial visits beginning with the Week 1 Visit will discontinue treatment and remain in the trial.

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

- Document gout flares and intensity.
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to the pegloticase infusion (See Section 9.5.4.4).
- Assess MTX compliance and re-dispense MTX.
- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis, and IR prophylaxis compliance.
- Fill gout prophylaxis, fexofenadine, acetaminophen, and folic acid prescriptions, as needed.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Administer IR prophylaxis (i.e., fexofenadine, acetaminophen, and methylprednisolone) (see Section 9.4.1.3).
- Administer pegloticase and record date, volume, and duration of infusion, and start/stop time of dosing and start/stop time of the 10-mL IV flush.

Post Infusion

- Obtain a post-infusion blood sample for sUA to be shipped to the Central Laboratory. (see Section 9.5.1.1).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) any time after the end of the infusion, but prior to discharge. (See Section 9.5.4.4).
- Inquire about AEs and concomitant medication use.

9.5.6.2.27 Week 45

- Assess MTX compliance and re-dispense MTX.
- Obtain blood sample for measurement of sUA (only 1 sample for central laboratory)
- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.

9.5.6.2.28 Week 46

- Assess MTX compliance.
- Obtain blood sample for measurement of sUA (only 1 sample for central laboratory)
- AE/SAE and Concomitant Medication data collection will occur at the subject's scheduled infusion visit or if spontaneously reported.

9.5.6.3 End of Pegloticase Infusions Visit

Subjects who end pegloticase infusions due stopping criteria or other reasons will complete the End of Pegloticase Infusions Visit procedures within 2 weeks of the last infusion. Subjects should continue to participate in all visits through the end of the trial. (See 9.3.3.1.1).

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

- Investigator review of clinical status and subject treatment goals.
- Document gout flares and intensity.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to discharge. (See Section 9.5.4.4).
- Record weight.
- Administer [redacted].
- [redacted].
- Assess MTX compliance and reconciliation.
- Ask Yes/No question regarding folic acid, gout flare prophylaxis compliance.
- [redacted]
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology and clinical chemistry analysis and hs-CRP.
- Obtain a urine sample for albumin:creatinine ratio.

- Obtain blood samples for pegloticase PK analysis.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies.
- Obtain optional urine and whole blood and serum samples from subjects who consent for future analysis.
- Obtain a blood sample (1 sample) for measurement of sUA.
- Inquire about AEs and concomitant medication use.

9.5.6.4 Week 24/Week 48/End of Trial/Early Termination Visit

- Investigator review of clinical status and subject treatment goals.
- Document gout flares and intensity.
- Perform a targeted physical examination (at a minimum this should include heart, lungs and abdominal examination).
- Record vital signs (blood pressure, respiratory rate, temperature, and heart rate) prior to discharge. (See Section 9.5.4.4).
- Record weight.
- Administer [redacted]
- [redacted].
- [redacted]
- Assess MTX compliance.
- Review dosing calendar for subjects that record the date and time they took MTX and record in the EDC. (Additional calendar pages may be provided at future visits as needed). Entries that to do not agree with the pill count should be addressed and corrected with the subject at this visit.
- Ask Yes/No question regarding folic acid compliance.
- Obtain a urine sample from all females of childbearing potential for performance of a pregnancy test.
- Obtain blood samples for hematology, clinical chemistry analysis, hs-CRP.

- Obtain a urine sample for albumin:creatinine ratio.
- Obtain blood samples for pegloticase PK analysis.
- Obtain blood samples for anti-PEG and anti-uricase IgG antibodies.
- Obtain optional urine and whole blood and serum samples from subjects who consent for future analysis.
- Obtain a blood sample (1 sample) for measurement of sUA.
- Inquire about AEs and concomitant medication use.

9.5.6.5 Safety Follow-up Phone/Email Visits

4 weeks after the last pegloticase infusion or MTX dose (whichever is later), subjects will be contacted by telephone or email to inquire about SAEs. Subjects who are females of childbearing potential will be asked to confirm that ovulation has occurred. If the subject has not ovulated, the subject will be requested to return to the site for a urine pregnancy test. Note: Subjects that agree to continue study visits post end of pegloticase visit will collect the 4 Wks post treatment follow up as part of the subjects continued visits. In the event a subject continues visits after the end of pegloticase but the visit is not at least 4 Wks post treatment then the safety follow-up phone call will still be required.

9.5.6.6 MTX Partner Pregnancy Follow-up

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

9.6 Statistical Methods and Determination of Sample Size

9.6.1 Endpoints

9.6.1.1 Primary Endpoints

The primary efficacy endpoints are:

1. Proportion of responders at Month 6 (Weeks 20, 21, 22, 23 and 24), defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6
2. Time to first sUA ≥6 mg/dL after first achieving sUA <6 mg/dL, from the first pegloticase infusion until Week 24

9.6.1.2 Secondary Endpoints

The secondary endpoints are:

1. Pharmacokinetic parameters (e.g., AUC, Cmax and C_{trough})
2. Proportion of subjects with sUA <6 mg/dL at each scheduled visit
3. Area under the sUA concentration vs time curve from Day 1 to Week 24 and Day 1 to Week 48
4. Proportion of the subjects sustained sUA< 6 mg/dL from Day 1 to Week 24 and Day 1 to Week 48
5. Proportion of subjects with anti-uricase antibodies and the proportion of subjects with anti-poly (ethylene glycol) antibodies and their titers at each scheduled visit

9.6.1.3 Exploratory Endpoints

The exploratory efficacy endpoints are:

9.6.1.4 Safety and Tolerability Endpoints

Safety and tolerability endpoints are:

1. Adverse Events:
    a. Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) regardless the relationship to trial drug and relationship, each
    b. Incidence of TEAEs leading to trial drug discontinuation
    c. Incidence of AESI: IRs, anaphylaxis, gout flares, and MACE including type I and type II non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure
2. Laboratory tests: changes in laboratory test results from baseline at each scheduled visit
3. Vital signs: changes from baseline at each scheduled visit

9.6.2 Analysis Sets

The following analysis populations will be defined for this trial:

- Intent-to-Treat (ITT) Analysis Set: all subjects who are enrolled and have at least one scheduled assessment done on Day 1.
- Per-protocol (PP) Analysis Set: all enrolled subjects who receive at least 1 dose of pegloticase, are taking the 15 mg dose of MTX at the time of first pegloticase dose, and have no major protocol deviations that would challenge the validity of the data
- Pharmacokinetic (PK) Analysis Set: all enrolled subjects who receive at least one dose of pegloticase and have a post-pegloticase sample evaluable for PK analysis
- Safety Analysis Set: all enrolled subjects who take at least one dose of pegloticase + MTX
- MTX Analysis Set: all subjects who take at least one dose of MTX

The ITT analysis set, defined above, will be used to assess efficacy endpoints. If the ITT analysis set and the PP analysis set are the same, then analysis results and summaries based

on only the ITT analysis set will be provided. The estimand for the primary analysis will use the Treatment Policy Strategy for most intercurrent events; selected intercurrent events leading to data that are missing completely at random may be addressed with a While-on-Treatment Strategy.

9.6.3 Demographic Variables

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

9.6.4 Subject Disposition

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

9.6.5 Efficacy Endpoint Analysis

The ITT analysis set will be used to assess efficacy endpoints. The estimand for the primary analysis will use the Treatment Policy Strategy for most intercurrent events; selected intercurrent events leading to data that are missing completely at random may be addressed with a While-on-Treatment Strategy.

9.6.5.1 sUA Endpoint Analysis

The proportion of time each subject's sUA is <6 mg/dL will be calculated using observed data during Month 3 (Weeks 10, 11, 12, 13, and 14), Month 6 (Weeks 20, 21,22, 23, and 24), Month 9 (Weeks 32, 34, and 36), and Month 12 (Weeks 44, 46, and 48). The amount of time that sUA is <6 mg/dL (using linear interpolation if necessary) will be calculated, and divided by the total amount of time from the first to the last observed sUA value in corresponding time range (missed values in this time range will be ignored for purposes of this calculation). Subjects who have no available sUA value in this time range will be imputed as non-responders unless the data are missing completely at random, in which case they will be omitted from the analysis. Two-sided exact 95% confidence intervals will be calculated.

Time from first infusion of pegloticase to the first observed sUA ≥6 mg/dL [redacted] after first achieving sUA<6 will be summarized using product-limit estimates. Subjects who never have an observed sUA value ≥6 mg/dL or two consecutive time will be censored at the time of their last observed sUA value. The median and quartiles, with associated two-sided 95% confidence intervals, will be calculated.

The proportion of subjects with sUA value <6 mg/dL at each scheduled assessment will be summarized. The proportion of subjects sustained sUA value to <6 mg/dL from Day 1 to Week 24 and Day 1 to Week 48 will be summarized. Subjects who have no available sUA value at a given scheduled assessment will be imputed as non-responders in the responder rate analysis

unless the data are missing completely at random, in which case they will be omitted from the analysis. Two-sided exact 95% confidence intervals will be calculated.

The area under the sUA curve from Day 1 to Week 24 and from Day 1 to Week 48 will be summarized using linear interpolation between observed data points.

One-at-a-time 95%, two-sided confidence intervals will be calculated for each parameter. No adjustment will be made for multiple endpoints or time points.

Data will be summarized on a regular basis for purposes of planning future cohorts, with no Type I error rate adjustments made due to multiple summaries.

[redacted]

9.6.6 Pharmacokinetic and Anti-drug Antibody Analysis

Concentrations and PK parameters for pegloticase and [redacted] (as appropriate) will be summarized using descriptive statistics for the PK population.

Incidence of anti-drug antibodies and titer levels at each scheduled assessment visit will be summarized.

Details will be provided in the statistical analysis plan.

9.6.7 Safety Analysis

Extent of exposure of MTX and extent exposure of pegloticase will be summarized for duration of treatment, number of doses administered. Number of interruptions and number of completed infusions with or without interruptions will be summarized for pegloticase.

Treatment-emergent AEs (TEAEs) during the MTX Run-In Period are defined as events with an onset date on or after the first dose of MTX through the first pegloticase infusion, or 4 weeks 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 4 weeks after the last dose of pegloticase and MTX (whichever is later). TEAEs that occur during the MTX Run-in Period prior to the first infusion of pegloticase (Day 1) will be summarized separately for the MTX population. TEAEs will be summarized for the safety population separately for the Run-In Period (Week -4 to Day -1) by dose cohort and overall (after through 4 weeks after the last dose of treatment)

The number of subjects experiencing at least one adverse event, at least one serious AE, at least one severe AE, and with an AE that leads to discontinuation of pegloticase or premature discontinuation of the trial will be summarized. The number and percentage of subjects

experiencing AEs will be summarized by system organ class and preferred term. Summaries by maximum severity and relationship to MTX and/or pegloticase will also be provided. SAEs and AEs leading to discontinuation of MTX and/or pegloticase will be presented by system organ class and preferred term. Similarly, SAEs and AEs leading to premature discontinuation of the trial will be presented, if applicable.

The proportion of subjects with SAEs and each AESI will be summarized by treatment cohort. The proportion of subjects experiencing an SAE and each AESI will be summarized for each treatment cohort, along with the treatment difference in proportions, corresponding 95% CI for the treatment difference.

Descriptive statistics of laboratory test results, including urine albumin:creatinine ratio, along with changes from baseline will be summarized at each scheduled by treatment cohort. Shift tables for laboratory parameters by Common Terminology Criteria for Adverse Events grade will be presented for those laboratory parameters with CTCAE grade defined. Laboratory test results will also be classified relative to the normal reference range (normal, low, or high).

Descriptive statistics of vital signs, including blood pressure, respiratory rate, temperature, and heart rate, along with changes from baseline will be summarized by at each scheduled visit by treatment cohort. Incidence of abnormal findings based on 12-Lead ECG will be summarized by cohort.

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, and for the Run-in and Pegloticase + MTX periods combined, where applicable.

9.6.8 Interim Analyses

There is no formal Interim Analysis.

Once the observations for the first two 4-week periods (i.e., Week 4 and Week 8) have been obtained from approximately the first 10 subjects in the first cohort, the data may be analyzed to determine:

1) No dose escalation with:

   a) additional subjects enrolled at the same dose in the first cohort, or

   b) change the infusion duration from 120 minutes to 60 minutes,

2) Dose escalation to between 24 mg and 32 mg Q4 Wks as the second cohort. The infusion duration may change from 120 minutes to 60 minutes.

3) Trial pause and re-evaluation for safety concerns.

This determination will be made based on assessment of the available 4- and 8-week PK, PD, efficacy, safety and tolerability data from the approximately first 10 subjects in the first cohort. If additional subjects are enrolled in Cohort 1, determination of the need and the dose for a second cohort will be made based on an additional analysis of available 4- and 8-week PK, PD, efficacy and safety data for all subjects in Cohort 1.

9.6.9 Sample Size and Power Considerations

A sample size of up to 40 subjects (approximately 10-20 subjects per dose cohort) is planned for this trial.

With approximately 10 subjects assessed at a given dose level, an observed response rate for a dichotomous endpoint of 70% (7/10) will provide a two-sided 95% confidence interval with a lower bound of approximately 35%. If 20 subjects are assessed at a given dose level, an observed response rate of 70% (14/20) will provide a two-sided 95% confidence interval with a lower bound of approximately 46%.

9.7 Changes in the Conduct of the Trial

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

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

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

10 SOURCE DOCUMENTATION AND INVESTIGATOR FILES

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

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

- Medical history/physical condition and diagnosis of the subject before involvement in the trial sufficient to verify that the subject meets protocol entry criteria.

- Trial number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed progress notes).
- Progress notes for each subject visit (each dated and signed).
- Records of each trial visit including each trial assessment and the identity of the staff member performing the assessment.
- Trial drug dispensing and return.
- Review by the Investigator or qualified personnel on the 1572 of laboratory test results.
- AEs (start and stop date, description, action taken, and resolution).
- Investigator or sub-investigator's signed assessment of AEs.
- Concomitant medications (start and stop dates, reason for use).
- Condition of subject upon completion of, or premature withdrawal from, the trial.

11 CASE REPORT FORMS

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

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

12 TRIAL MONITORING

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

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

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

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

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

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

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

13 DATA MANAGEMENT

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

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

15 PUBLICATION

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

16 REFERENCES

Albert JA, Hosey T, LaMoreaux B. Increased Efficacy and Tolerability of Pegloticase in Patients With Uncontrolled Gout Co-Treated With Methotrexate: A Retrospective Study. Rheumatology and Therapy. 2020;(7):639–48

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

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

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

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

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

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

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

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

Calabrese et al. Arthritis Research & Therapy (2017) 19:191

FitzGerald JD et al. American College of Rheumatology Guideline for the Management of Gout. Arthritis Care & Research. 2020 Jun;72(6):744-60

Food and Drug Administration. Center for Drug Evaluation and Research, Division of Anesthesia, Analgesia, and Rheumatology Products. AAC Briefing Document Krystexxa (Pegloticase). 2009. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM165714.pdf. [Accessed 2018 May 31].

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

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

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

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

Khanna P et al. Reducing immunogenicity of pegloticase (RECIPE) with concomitant use of mycophenolate mofetil in patients with refractory gout – a phase II double blind randomized controlled trial, ACR Convergence 2020, Abstract 0952.

Khanna P et al. Reducing immunogenicity of pegloticase (RECIPE) with concomitant use of mycophenolate mofetil in patients with refractory gout – a phase II double blind randomized controlled trial, ACR Convergence 2020, Oral Presentation.

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

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

Lipsky PE, Calabrese LH, Kavanaugh A, et al. Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout. Arthritis Res Ther 2014;16:R60.

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

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

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

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

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

Saag KG, Fitz-Patrick D, Kopicko J, et al. Lesinurad combined with allopurinol: a randomized, double-blind, placebo-controlled study in gout patients with an inadequate response to standard-of-care allopurinol (a US-based study). Arthritis Rheumatol 2017;69:203–12.

Saag K, Feinman M, Kititz AJ, Baraf HSB, Fleischmann R, Kavanaugh A, Lipsky PE. Initial results of a clinical study to determine whether a tolerizing regimen of pegloticase can increase the frequency of subjects having sustained lowering of serum utate [abstract]. Arthritis Rheumatol 2017;69(suppl 10)

Saag K, Feinman M, Baraf HS, Fleischmann R, Kavanaugh A, Lipsky P. The regimen of Pegloticase administration can increase the frequency of subjects having sustained lowering of serum urate. Ann Rheum Dis 2018;77(Suppl 2) FRI0240.

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

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

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

Song Y et al. Pharmacokinetics of pegloticase and methotrexate polyglutamate(s) in patients with uncontrolled out receiving pegloticase and co-treatment of methotrexate. ACR Convergence 2020, Abstract 0683.

Song Y et al. Pharmacokinetics of pegloticase and methotrexate polyglutamate(s) in patients with uncontrolled out receiving pegloticase and co-treatment of methotrexate. ACR Convergence 2020, Poster Presentation E001549.

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

Sundy JS, Ganson NJ, Kelly SJ, et al. Pharmacokinetics and pharmacodynamics of intravenous PEGylated recombinant mammalian urate oxidase in patients with refractory gout. Arthritis Rheum 2007 Mar;56(3):1021-1028

Sundy JS, Becker MA, Baraf HSB, Barkhuizen A, Moreland LW, Huang W, Waltrip RW, Maroli AN, Horowitz Z. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a Phase II randomized study. Arthritis & Rheumatism 2008; 58(9):2882-2991 DOI 10.1002/art.23810

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

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

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

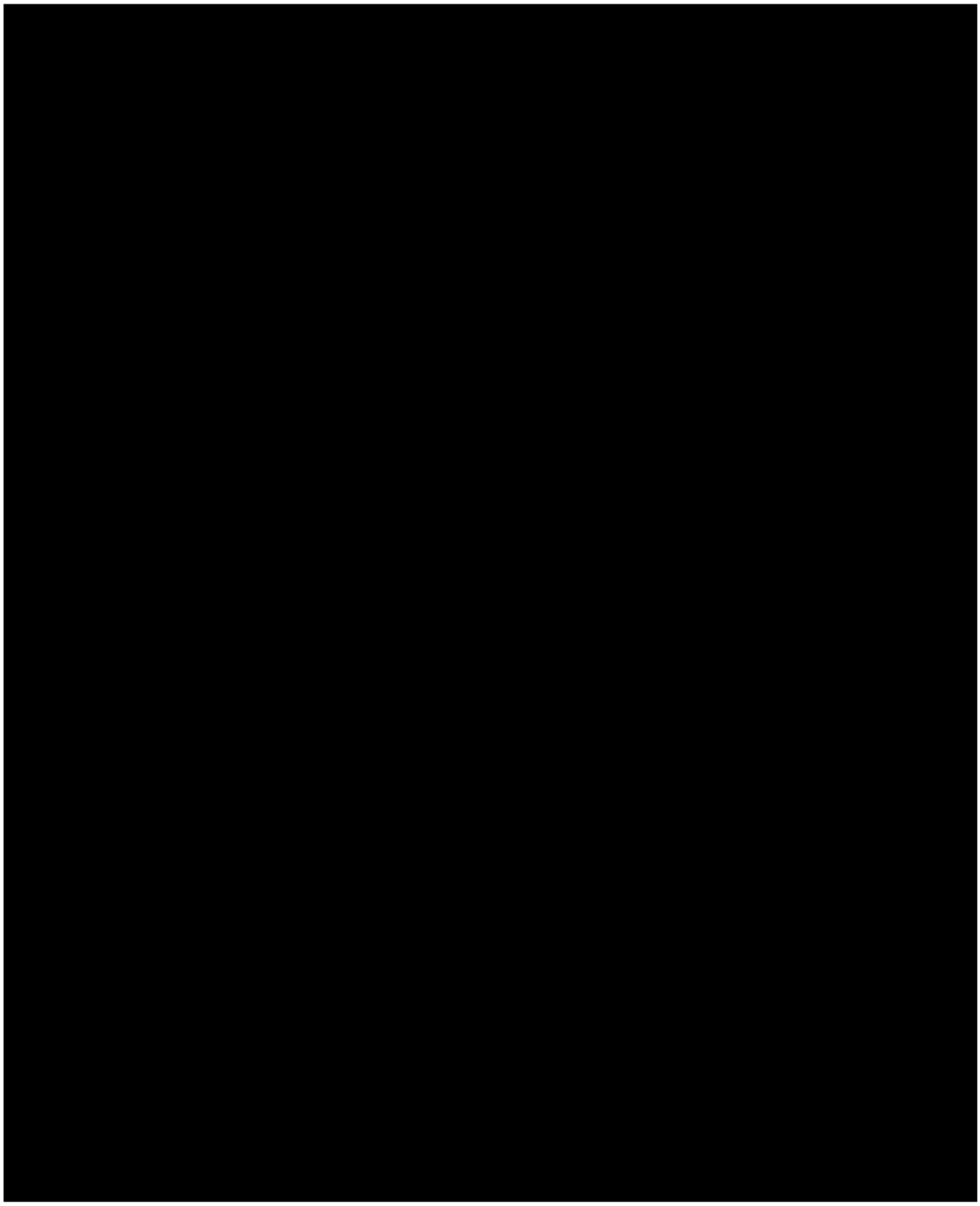
Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011;63(10):3136-41.

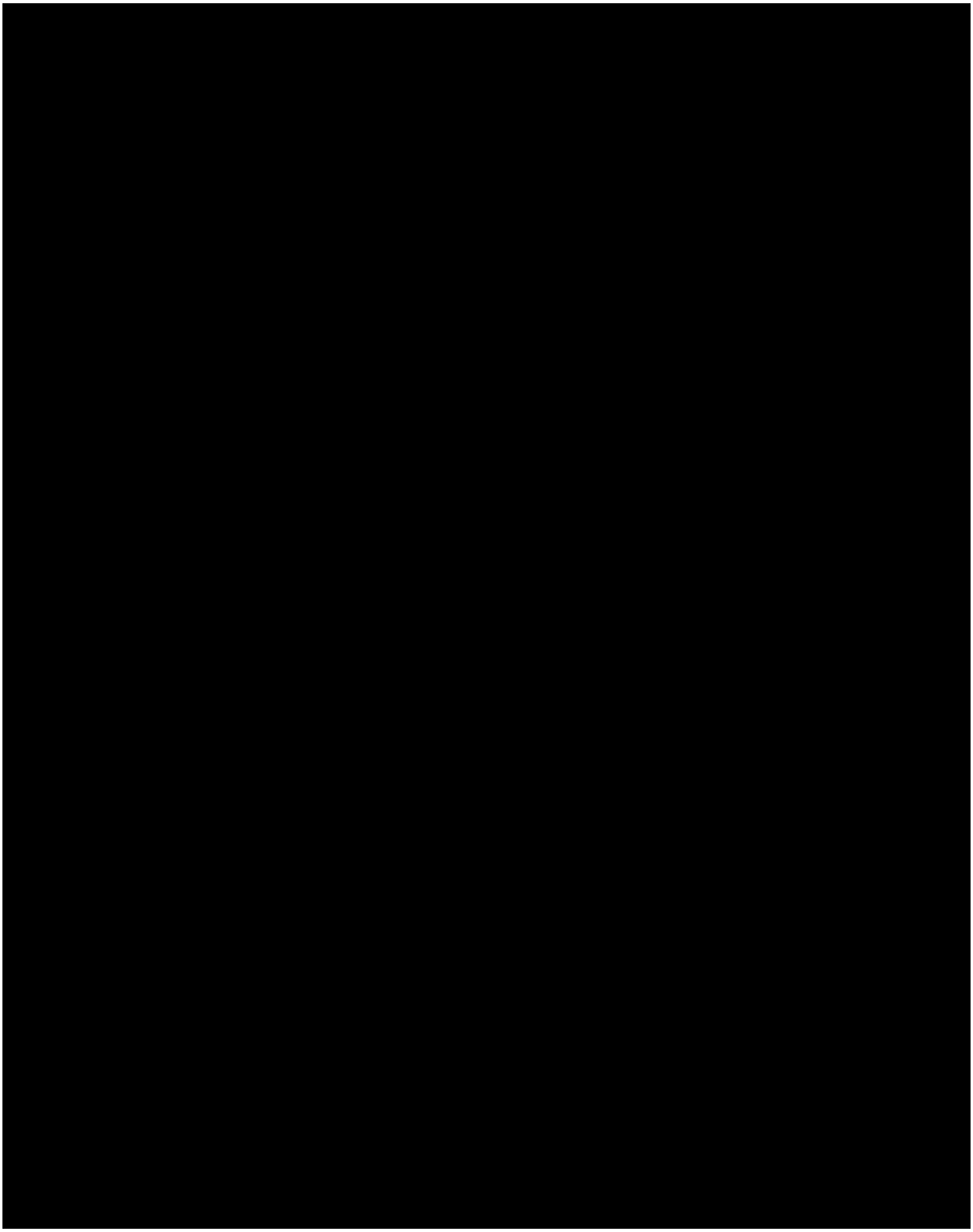
17 APPENDICES

17.1 Administrative Appendix

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

Medical Monitor	[redacted], MD Senior Medical Director R&D Clinical Development 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 Investigator Assessment of Clinical Status

Instructions: The Investigator or designee will document the following questions and responses in regards to clinical status in the subject source documents at the protocol specified visits.

[redacted]	
2. Presence of chronically swollen joints due to gout?	Yes No
3. Presence of chronic joint pain attributed to gout?	Yes No
4. Are there symptoms the subject is specifically seeking to improve (treatment goals)	Yes No
~If yes to question 4, select all that apply for symptoms the subject is seeking to improve:	[redacted] Frequency of flares Chronic joint swelling attributed to gout Chronic joint pain attributed to gout Other (specify):_____