



Protocol Title: A Phase 4, Randomized, Double-blind, Multicenter Non-inferiority Trial Evaluating the Efficacy and Safety of Intravenous KRYSTEXXA[®] (pegloticase) Administered Every 4 Weeks Compared with KRYSTEXXA Administered Every 2 Weeks with Co-administration of Weekly Doses of Methotrexate, Followed by an Open-label Extension, in Participants with Uncontrolled Refractory Gout (FORWARD II)

Protocol Number: HZNP-KRY-409

Version: 2.0

Compounds: KRYSTEXXA (recombinant modified mammalian urate oxidase [uricase]) and methotrexate (MTX)

Indication: Chronic gout in adult patients refractory to conventional therapy

Brief Title: A trial to investigate the non-inferiority of pegloticase administered every 4 weeks (Q4W) with MTX compared with every 2 weeks (Q2W) with MTX in participants with uncontrolled refractory gout

Trial Phase: 4

Sponsor Name: Horizon Therapeutics Ireland DAC

Legal Registered Address: 70 St. Stephen's Green, Dublin 2 Ireland D02 E2X4

IND Number: 010122

Date of Protocol: 06 March 2024

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), and applicable local regulations. The Principal Investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB)/Research Ethics Board (REB), except where necessary to eliminate an immediate hazard to the trial participants. All personnel involved in the conduct of this trial have completed ICH GCP training. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/REB before the changes are implemented to the trial. All changes to the consent form will be IRB/REB approved.

SPONSOR SIGNATURE PAGE

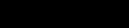
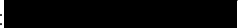
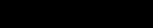
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Protocol Title: A Phase 4, Randomized, Double-blind, Multicenter Non-inferiority Trial Evaluating the Efficacy and Safety of Intravenous KRYSTEXXA[®] (pegloticase) Administered Every 4 Weeks Compared with KRYSTEXXA Administered Every 2 Weeks with Co-administration of Weekly Doses of Methotrexate, Followed by an Open-label Extension, in Participants with Uncontrolled Refractory Gout (FORWARD II)

Version Date: 06 Mar 2024

Approved by:

Clinical Development Representative		
Name:	Title:	Signature and Date:
 MD	Senior Medical Director, Clinical Development	DocuSigned by:   Signer Name:  Signing Reason: I approve this document Signing Time:  
Biostatistics Representative		
Name:	Title:	Signature and Date:
 MS	Director, Biostatistics	DocuSigned by:   Signer Name:  Signing Reason: I approve this document Signing Time:  

INVESTIGATOR'S AGREEMENT

Protocol Number: HZNP-KRY-409

Version: 2.0

Version Date: 06 Mar 2024

I have read the protocol, appendices, and accessory materials related to Study **HZNP-KRY-409 (FORWARD II); A trial to investigate the non-inferiority of pegloticase administered Q4W with MTX compared with Q2W with MTX in participants with uncontrolled refractory gout**, and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products (IPs) provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and GCP as outlined by ICH
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study specific procedures or administering IPs to those participants
- To maintain records of each participant's participation and all data required by the protocol

Name:	Title:	Institution:
Signature:		Date:

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
Protocol Amendment 1	06 Mar 2024
Original Protocol	10 Oct 2023

Overall Rationale for Amendment 1:

The overall rationale for amending the protocol is to increase the sample size in order to increase the statistical power of the trial from 85% to 90% for demonstrating the non-inferiority of pegloticase administered Q4W with MTX compared to pegloticase administered Q2W with MTX in participants with uncontrolled refractory gout. Additionally, updates were made incorporating FDA feedback on the protocol regarding margin justification and the analysis method for the primary endpoint.

The major changes in this amendment are described in the table below. Administrative changes were made throughout the document and not listed in the table below.

Original text including Section Number	Amended text including Section Number	Brief Rationale
Sponsor Signature Page (Biostatistics Representative) [REDACTED], Senior Biostatistician	Sponsor Signature Page (Biostatistics Representative) [REDACTED], <i>Director Biostatistics</i>	<i>Updated to reflect biostatistics representative signatory change.</i>
Synopsis (Brief Summary) and Section 8.7 Mechanistic/Disease Biomarkers Samples for measurement of sUA levels, PK analysis of pegloticase, pegloticase immunogenicity and MTX polyglutamate analysis will be collected at visits indicated in Section 1.3. No evaluation of mechanistic/disease biomarkers is planned.	Synopsis (Brief Summary) and Section 8.7 Mechanistic/Disease <i>7Exploratory</i> Biomarker <i>Evaluation</i> Samples for measurement of sUA levels, PK analysis of pegloticase, pegloticase immunogenicity, MTX polyglutamate <i>and biomarker</i> analysis will be collected at visits indicated in Section 1.3. <i>Serum, plasma, and urine will be assessed for biomarkers related to the mechanism of action of pegloticase and factors associated with gout activity. Intended purpose and biomarker analysis include but are not limited to the proteomic evaluation of gout-flare inflammatory mediators and cardiometabolic markers to inform trial findings (as needed), Serum, plasma and urine will be collected during Screening and prior to pegloticase/placebo for pegloticase infusion at Day 1, Weeks 2, 4, 8, 12 and 24, and at any time during the Week 48/ET/EOT and 3M FU visits. Remaining exploratory biomarker samples may be used for future research.</i> <i>For subjects where no Day 1 pre-infusion samples were collected, biomarker samples will not be collected at the subsequent visits.</i> <i>Each sample collection date and time will be recorded in source documents.</i> <i>Detailed instructions regarding blood and urine sample timing and handling are provided in the Laboratory Manual.</i>	<i>Updated to reflect the addition of biomarker samples for analysis to inform KRYSTEXXA trial findings and profile dynamics of uncontrolled gout and associated co-morbidities in response to pegloticase infusion once every 4 weeks.</i>

Synopsis (Number of Participants) and 9.5 Sample Size Determination and 10.1.8 Investigator and Trial Administrative Structure Approximately 206 participants (103 in each treatment group during the 24-week double-blind period) will be enrolled (i.e., receive at least 1 dose of pegloticase on Day 1) at approximately 65 sites in the United States (US). The trial will be conducted at approximately 65 sites in the US.	Synopsis (Brief Summary) and 9.5 Sample Size Determination and 10.1.8 Investigator and Trial Administrative Structure Approximately 240 participants (120 in each treatment group during the 24-week double-blind period) will be enrolled (i.e., receive at least 1 dose of pegloticase on Day 1) at approximately 70 sites in the United States (US). The trial will be conducted at approximately 70 sites in the US.	<i>Updated the number of subjects to support increased statistical power and increased number of sites to support study enrollment.</i>
Synopsis (Statistical Analyses) Sample Size Determination and 9.5 Sample Size Determination With a non-inferiority margin set at 20%, this sample size achieves 85% power, assuming a responder rate of 65% in both groups at the 1-sided Type I error rate of 0.025. Previous registration trials indicated a responder rate of approximately 44% in the pegloticase monotherapy group, while the placebo group had no responders. In the MIRROR-RCT trial (HZNP-KRY-202), the pegloticase 8 mg Q2W + MTX co-administration group exhibited a responder rate of 71%, and it is anticipated that the active-controlled group will have a responder rate of about 65%-70%. Considering an effect size of 65% compared with placebo, a non-inferiority margin of 20% was chosen to preserve the similar amount of the effect observed in the active-controlled group compared with the pegloticase monotherapy group.	Synopsis (Statistical Analyses) Sample Size Determination and 9.5 Sample Size Determination With a non-inferiority margin set at 20%, this sample size achieves 90% power, assuming a responder rate of 65% in both groups at the 1-sided Type I error rate of 0.025. <i>deleted</i>	<i>Increased statistical power for the study and moved margin justification from sample size determination section to Section 9.3.2.</i>
Synopsis (Statistical Analysis Methods) Efficacy and 9.3.2 Primary Efficacy Endpoint Analysis The analysis of the primary endpoint for Month 6 responder rate will assess risk difference (difference in response proportions) in a stratified analysis. The analysis	Synopsis (Statistical Analysis Methods) Efficacy and 9.3.2 Primary Efficacy Endpoint Analysis The primary endpoint will <i>be analyzed using g-computation to estimate the covariate adjusted unconditional treatment effect with 95% CI (Ye et al., 2023). Logistic regression will be used as the working model in the g-computation</i>	<i>Updated to reflect a change in the analysis method and a change in margin for the tophi endpoint (in synopsis). Justification for margin for primary endpoint moved from</i>

will use Cochran-Mantel-Haenszel (CMH) weighting to estimate the common risk difference within strata (presence of tophi [yes, no]) and to estimate the standard error of the common risk difference. The difference in response rates, comparing pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX, will be estimated along with the corresponding 95% confidence interval (CI). The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups is less than the non-inferiority margin of 20%. The difference in the proportion of participants with resolution of ≥ 1 tophus (100% decrease in the area of at least 1 tophus) at Week 24 between pegloticase 16 mg Q4W with MTX and pegloticase 8 mg Q2W with MTX will be tested with a chi-square test, and the difference in rates will be estimated along with the corresponding 95% CI. The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups is less than the non-inferiority margin of 20%.	<i>procedure with treatment and covariates (including but not limited to) for tophi presence (present, not present), age, and baseline eGFR.</i> The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups is less than the non-inferiority margin of 20%. The proportion of participants with resolution of ≥ 1 tophus (100% decrease in the area of at least 1 tophus) at Week 24 will <i>be analyzed using the same g-computation procedure used for the primary endpoint to estimate the covariate adjusted unconditional treatment effect with 95% CI.</i> Logistic regression will be used as the working model in the <i>g-computation procedure with treatment and covariates (including but not limited to) for age, and baseline eGFR.</i> The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups is less than the non-inferiority margin of 15%. <i>Previous registrational trials indicated a responder rate of approximately 44% in the pegloticase monotherapy group, while the placebo group had no responders. In MIRROR-RCT (NCT0399473), the pegloticase 8 mg Q2W + MTX co-administration group exhibited a responder rate of 74% (95% CI: 64%, 82%) compared to a 41% responder rate in the pegloticase 8 mg Q2W monotherapy group (between-group difference [95% CI]: 33% [17%, 49%]) in participants who received pegloticase. This trial will enroll participants from the same gout population as MIRROR-RCT and has a nearly identical study design as well as inclusion and exclusion criteria. The primary endpoint (the proportion of responders during Month 6) is the same as the MIRROR-RCT primary endpoint, and missing data and intercurrent events will be handled in the same manner. Therefore, it is reasonable to anticipate that the active-</i>	<i>sample size determination sections to Section 9.3.2.</i>
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	<i>controlled group will have a responder rate similar to that of MIRROR-RCT.</i> <i>There are no prior trials comparing pegloticase co-administered with MTX vs. placebo. However, patients with uncontrolled gout would not be expected to maintain sUA < 6 mg/dL without treatment and so a 0% response rate in untreated patients, as seen in the registrational trials, is reasonable. Considering an effect size of 65% compared with placebo, a non-inferiority margin of 20% was chosen to preserve 69% of the effect vs. placebo, and also a similar amount of the effect observed in the active-controlled group compared with the pegloticase monotherapy group</i>	
Synopsis (Data Monitoring/Other Committee)	Synopsis (<i>Adjudication</i> Committee)	Updated to clarify the section title name.
Schema N=103 per arm in the Double-blind period; N=206 in the Open-label extension	Schema N= <i>120</i> per arm in the Double-blind period; N= <i>240</i> in the Open-label extension	Updated to reflect the increase in subject numbers.
Schedule of Activities (SoA) <i>None</i>	Schedule of Activities (SoA) <i>Plasma and serum sample for biomarker analysis, and Urine samples for biomarker analysis added at Screening, Day 1, Weeks 2, 4, 8, 12, 24, Week 48/ET/EOT and 3M FU visit.</i> Added Footnote <i>q</i>: <i>Plasma, serum, and urine samples for biomarker analysis will be collected at Screening, prior to the pegloticase/placebo for pegloticase infusion at Day 1 and Weeks 2, 4, 8, 12, 24, and at any time during Week 48 and 3M FU visits. For subjects where no Day 1 pre-infusion samples were collected, biomarker samples will not be collected at the subsequent visits.</i>	<i>Collect data to inform a baseline biomarker profile for uncontrolled gout and KRYSTEXXA</i>
Schedule of Activities (SoA) Footnote <i>q</i>: Serum samples for measurement of sUA levels will be collected and sent to the central laboratory at the Screening Visit, the Week -4 Visit (prior to the first dose of MTX) and the Week -2 Visit during the MTX Run-in	Schedule of Activities (SoA) Updated to Footnote <i>r</i>: Serum samples for measurement of sUA levels will be collected and sent to the central laboratory at the Screening Visit, the Week -4 Visit (prior to the first dose of MTX) and the Week -2 Visit during the MTX Run-in Period. <i>On all</i>	<i>Administrative change – revision to the language for easier readability.</i>

Period. On Day 1, pre-infusion and post-infusion sUA samples will be collected to be shipped to the central laboratory. For the remainder of trial visits beginning at Week 2 during the double-blind and open-label extension Pegloticase + MTX Periods, 1 sUA sample will be collected within 48 hours PRIOR to each infusion visit until the Week 44 Visit for determination by a local laboratory if the sUA discontinuation criterion has been met. A post-infusion sUA blood sample will additionally be collected on Day 1 and at all infusion visits for same-day shipment to the central laboratory. Additional serum samples for sUA levels will be collected at non-infusion visits at Weeks 21, 23, 26, 30, 34, 38, 42, 46, the End of Pegloticase Infusions Visit (if applicable), the Week 48/EOT/ET Visit and 3-month Follow-up Visit. See the Laboratory Manual for instructions.	<i>infusion visit dates starting at Day 1, a pre-infusion and post-infusion sUA will be collected to be shipped to the Central Laboratory. Additional serum samples for sUA levels will be collected at non-infusion visits at Weeks 21, 23, 26, 30, 34, 38, 42, 46, the End of Pegloticase Infusions Visit (if applicable), the Week 48/EOT/ET Visit and 3-month Follow-up Visit and sent to the Central Laboratory. For all infusion visits beginning at Week 2 during the double-blind and open-label extension Pegloticase + MTX Periods, 1 sUA sample will be collected locally within 48 hours PRIOR to each infusion visit until the Week 44 Visit for determination by a local laboratory if the sUA discontinuation criterion has been met. See the Laboratory Manual for instructions.</i>	
Schedule of Activities (SoA) Footnote r & s Footnote r Participants will be assessed for elevated blood glucose and symptoms of hyperglycemia pre and post methylprednisolone infusion via finger prick test. Continuous monitoring is required for those undergoing treatment with pegloticase. Participants with clinically significant hyperglycemia (as determined by Investigators and/or Sponsor) or pre-existing diabetes must be under appropriate glycemic control before and while receiving pegloticase. Additional information including relevant medical history and HbA1c level must be collected for participants with clinically significant hyperglycemia. Footnote s: HbA1c testing must be performed at Screening for all participants. If HbA1c > 6.5% and/or if participant has known diagnosis of diabetes mellitus, additional measures including HbA1c every 3 months during the trial.	Schedule of Activities (SoA) Footnote s (Footnote r and Footnote s from the original protocol are now combined into Footnote s, and the language is updated): <i>HbA1c testing must be performed at Screening for all participants. If HbA1c > 6.5% and/or if participant has known diagnosis of diabetes mellitus, additional measures will be taken during the trial including HbA1c every 3 months. Additionally, participants that are diabetic or with elevated HbA1c's at Screening will be assessed for elevated blood glucose and symptoms of hyperglycemia prior to methylprednisolone infusion and after pegloticase infusion via finger prick test. Continuous monitoring is required for those undergoing treatment with pegloticase. Participants with clinically significant hyperglycemia (as determined by Investigators and/or Sponsor) or preexisting diabetes must be under appropriate glycemic control before and while receiving pegloticase. Additional information including relevant medical history and HbA1c level must be</i>	<i>Updated the text to clarify the requirements for HbA1c testing blood glucose finger prick testing throughout the trial.</i>

	<i>collected for participants with clinically significant hyperglycemia.</i>	
Schedule of Activities (SoA)	Schedule of Activities (SoA)	<i>sUA is not required at the 30 day visit.</i>
sUA indicated at 30 day visit	sUA deleted at 30 day visit; sUA added at 3 Month visit	
6.1.3 Pegloticase At the end of the infusion, the IV line will be flushed with 10 mL of normal saline to ensure the full dose is administered. The date and time of infusion start and stop (inclusive of the IV flush) will be recorded. Placebo for pegloticase will be 250 mL of 0.45% or 0.9% Sodium Chloride Infusion, USP and will be infused over approximately 120 ± 15 minutes while the participant is under close observation for any signs of distress. If an in-line filter is used, it should be 0.2 µm or larger. At the end of the infusion, the IV line will be flushed with 10 mL of normal saline to ensure the full dose is administered. The date and time of infusion start and stop (inclusive of the IV flush) will be recorded.	6.1.3 Pegloticase At the end of the infusion, the IV line will be flushed with 10 mL of normal saline <i>over ~15 min</i> to ensure the full dose is administered. The date and time of infusion start and stop <i>and the date and time</i> of IV flush <i>start and stop</i> will be recorded. Placebo for pegloticase will be 250 mL of 0.45% or 0.9% Sodium Chloride Infusion, USP and will be infused over approximately 120 ± 15 minutes while the participant 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 <i>over ~15 min</i> to ensure the full dose is administered. The date and time of infusion start and stop <i>and the date and time</i> of the IV flush <i>start and stop</i> will be recorded.	<i>Updated to clarify IV flush details for the pegloticase/placebo for pegloticase infusion.</i>
6.1.4 Gout Flare Prophylaxis none	6.1.4 Gout Flare Prophylaxis <i>Other gout-flare prophylaxis may be allowed if agreed upon by the Sponsor.</i>	<i>Added to allow other types of gout flare prophylaxis.</i>
6.6.2 MTX Dose Titration Algorithm and Intolerance Criteria During the <i>MTX Run-in</i> and double-blind and open-label extension Pegloticase + MTX Periods, MTX dose guidance based on new laboratory findings or new symptoms is summarized in Table 2.	6.6.2 MTX Dose Titration Algorithm and Intolerance Criteria During the double-blind and open-label extension Pegloticase + MTX Periods, MTX dose guidance based on new laboratory findings or new symptoms is summarized in Table 2.	<i>Updated to reflect MTX dose titrations made only during the double blind and open-label extension pegloticase + MTX periods.</i>

Table 2 Title: MTX Dose Guidance Based on New Laboratory Findings or New Symptoms During the <i>Run-in and</i> Double-blind and Open-label Extension Pegloticase + MTX Periods	Table 2 Title: MTX Dose Guidance Based on New Laboratory Findings or New Symptoms During the Double-blind and Open-label Extension Pegloticase + MTX Periods	
7.4.2 Centers	7.4.2 Centers	<i>Updated to complete the statement.</i>
A center may be closed and/or replaced for excessively slow recruitment or poor protocol adherence.	A center may be closed and/or replaced for excessively slow recruitment, poor protocol adherence, <i>or other reason as necessary according to the Sponsor.</i>	
8.2.1 Serum Uric Acid	8.2.1 Serum Uric Acid	<i>Administrative change – revision to the language for easier readability.</i>
On Day 1, pre-infusion and post-infusion sUA <i>samples</i> will be collected to be shipped to the central laboratory. For the remainder of trial visits beginning at Week 2 during the double-blind and open-label extension Pegloticase + MTX Periods, 1 sUA sample will be collected within 48 hours PRIOR to each infusion visit until the Week 44 Visit for determination by a local laboratory if the sUA discontinuation criterion has been met. A post-infusion sUA blood sample will additionally be collected on Day 1 and at all infusion visits for same-day shipment to the central laboratory. See the Laboratory Manual for instructions.	On <i>all infusion visit dates starting at</i> Day 1, a pre-infusion and post-infusion sUA will be collected to be shipped to the Central Laboratory. <i>Additional serum samples for sUA levels will be collected at non-infusion visits at Weeks 21, 23, 26, 30, 34, 38, 42, 46, the End of Pegloticase Infusions Visit (if applicable), the Week 48/EOT/ET Visit and 3-month Follow-up Visit and sent to the Central Laboratory.</i> For <i>all infusion visits</i> beginning at Week 2 during the double-blind and open-label extension Pegloticase + MTX Periods, 1 sUA sample will be collected locally within 48 hours PRIOR to each infusion visit until the Week 44 Visit for determination by a local laboratory if the sUA discontinuation criterion has been met. See the Laboratory Manual for instructions.	
Participants with an sUA level > 6 mg/dL at 2 consecutive trial visits beginning with the Week 2 Visit will discontinue pegloticase but remain in the trial to complete the scheduled assessments.	Participants with <i>a pre-infusion</i> sUA level > 6 mg/dL at 2 consecutive trial visits beginning with the Week 2 Visit will discontinue pegloticase but remain in the trial to complete the scheduled assessments.	<i>Updated to reflect a clarification that this refers to a pre-infusion sUA result.</i>

8.3.4 Clinical Safety Laboratory Tests Guidance on Blood Glucose Monitoring: participants will be assessed and monitored for elevated blood glucose and symptoms of hyperglycemia prior to and after methylprednisolone infusion. Glucose levels will be measured via finger prick test. HbA1c testing must be performed at Screening for all participants.	8.3.4 Clinical Safety Laboratory Tests Guidance on Blood Glucose Monitoring: <i>HbA1c testing must be performed at Screening for all participants. Participants who are diabetic and/or with elevated HbA1c at Screening</i> will be assessed and monitored for elevated blood glucose and symptoms of hyperglycemia prior to and after methylprednisolone infusion. Glucose levels will be measured via finger prick test.	<i>Updated to clarify HbA1c testing and additional blood glucose finger prick testing requirements.</i>
8.7 Mechanistic/Disease Biomarkers	8.7 Mechanistic/Disease <i>and Exploratory</i> Biomarker <i>Evaluation</i>	<i>Changes described in synopsis above.</i>
9.3.2 Primary Efficacy Endpoint Analysis	9.3.2 Primary Efficacy Endpoint Analysis	<i>Changes described in synopsis above.</i>
9.3.3 Secondary Endpoint Analysis:	9.3.3 Secondary Endpoint Analysis:	<i>Updated to reflect a change in the analysis method, changing the margin for tophi endpoint from</i>

9.3.3.1 Proportion of Participants with Complete Resolution of ≥ 1 Tophus (Using [REDACTED]) at Week 24 in Participants with Tophi at Baseline The primary estimand for the proportion of participants with complete resolution of ≥ 1 tophus at Week 48 is defined by the following: <table><tr><td>Population</td><td>FAS with tophus (or tophi) present at Baseline</td></tr><tr><td>ICE</td><td>Early discontinuation of pegloticase</td></tr><tr><td>ICE strategy</td><td>Tophi data collected after a participant has discontinued from pegloticase will be included in analysis.</td></tr><tr><td>Population-level summary</td><td>Difference in the proportion of participants with complete resolution of ≥ 1 tophus at Week 24 between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX</td></tr></table> The difference in the proportion of participants with resolution of ≥ 1 tophus (100% decrease in the area of at least 1 tophus) at Week 24 between pegloticase 16 mg Q4W with MTX and pegloticase 8 mg Q2W with MTX will be tested with a chi-square test, and the difference in rates will be estimated along with the corresponding 95% CI. The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups is less than the non-inferiority margin of 20%.	Population	FAS with tophus (or tophi) present at Baseline	ICE	Early discontinuation of pegloticase	ICE strategy	Tophi data collected after a participant has discontinued from pegloticase will be included in analysis.	Population-level summary	Difference in the proportion of participants with complete resolution of ≥ 1 tophus at Week 24 between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX	Section 9.3.3.1 title <i>deleted</i> The primary estimand <i>for this endpoint</i> is defined by the following: <table><tr><td>Population</td><td>FAS with tophus (or tophi) present at Baseline</td></tr><tr><td>ICE</td><td>Early discontinuation of pegloticase</td></tr><tr><td>ICE strategy</td><td>Tophi data collected after a participant has discontinued from pegloticase will be included in analysis.</td></tr><tr><td>Population-level summary</td><td>Difference in the proportion of participants with complete resolution of ≥ 1 tophus at Week 24 between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX</td></tr></table> <i>The proportion of participants with resolution of ≥ 1 tophus (100% decrease in the area of at least 1 tophus) at Week 24 will be analyzed using the same g-computation procedure used for the primary endpoint to estimate the covariate adjusted unconditional treatment effect with 95% CI. Logistic regression will be used as the working model in the g-computation procedure with treatment and covariates (including but not limited to) for age, and baseline eGFR. The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups is less than the non-inferiority margin of 15%.</i> <i>In MIRROR-RCT (NCT0399473), the pegloticase 8 mg Q2W + MTX co-administration group exhibited a tophus resolution rate of 35% at Week 24 compared to 13% in the pegloticase 8 mg Q2W monotherapy group (between-group</i>	Population	FAS with tophus (or tophi) present at Baseline	ICE	Early discontinuation of pegloticase	ICE strategy	Tophi data collected after a participant has discontinued from pegloticase will be included in analysis.	Population-level summary	Difference in the proportion of participants with complete resolution of ≥ 1 tophus at Week 24 between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX	<i>20% to 15% and adding justification for the margin.</i>
Population	FAS with tophus (or tophi) present at Baseline																	
ICE	Early discontinuation of pegloticase																	
ICE strategy	Tophi data collected after a participant has discontinued from pegloticase will be included in analysis.																	
Population-level summary	Difference in the proportion of participants with complete resolution of ≥ 1 tophus at Week 24 between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX																	
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ICE	Early discontinuation of pegloticase																	
ICE strategy	Tophi data collected after a participant has discontinued from pegloticase will be included in analysis.																	
Population-level summary	Difference in the proportion of participants with complete resolution of ≥ 1 tophus at Week 24 between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX																	

	<i>difference [95% CI]: 21% [3%, 39%]) in participants with tophi at baseline (N=52 and 29, respectively). While there are no prior placebo-controlled trials with the active control, untreated patients would not be expected to have tophus resolution. Considering an effect size of 30% compared with placebo, a non-inferiority margin of 15% was chosen to preserve 50% of the effect vs. placebo.</i>	
9.5 Sample Size Determination	9.5 Sample Size Determination	<i>Changes described in synopsis above.</i>
10.1.8 Investigators and Trial Administrative Structure	10.1.8 Investigators and Trial Administrative Structure	<i>Changes described in synopsis above.</i>
11 References <i>None</i>	11 References <i>Ye T, Bannick M, Yi Y, Shao J. Robust Variance Estimation for Covariate-Adjusted Unconditional Treatment Effect in Randomized Clinical Trials with Binary Outcomes. Stat Theory Relat Fields. 2023;7(2):159-163. doi: 10.1080/24754269.2023.2205802. Epub 2023 Apr 28. PMID: 37997606; PMCID: PMC10665030.</i>	<i>Reference added to support the analysis method.</i>

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	End-of-Trial
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IND	Investigational New Drug
IP	investigational product
IR	infusion reaction
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous(ly)
LLN	lower limit of normal
MACE	major adverse cardiovascular event(s)
MAS	MTX Analysis Set
MDRD	Modified Diet in Renal Disease
MTX	methotrexate
PEG	polyethylene glycol
PK	pharmacokinetic(s)
Q2W	every 2 weeks

Abbreviation	Definition
Q4W	every 4 weeks
REB	Research Ethics Board
SAE	serious adverse event
SAS	Safety Analysis Set
sBLA	supplemental Biologics License Application
sUA	serum uric acid
TEAE	treatment-emergent adverse events
ULN	upper limit of normal
ULT	urate-lowering therapy
US	United States
USP	United States Pharmacopeia
VAS	visual analog scale

Abbreviations that appear only in figures, tables and a single paragraph are defined with the relevant figures, tables and paragraphs.

1 **PROTOCOL SUMMARY**

1.1 **Synopsis**

Protocol Title: A Phase 4, Randomized, Double-blind, Multicenter Non-inferiority Trial Evaluating the Efficacy and Safety of Intravenous KRYSTEXXA[®] (pegloticase) Administered Every 4 Weeks Compared with KRYSTEXXA Administered Every 2 Weeks with Co-administration of Weekly Doses of Methotrexate, Followed by an Open-label Extension, in Participants with Uncontrolled Refractory Gout (FORWARD II)

Brief Title: A trial to investigate the non-inferiority of pegloticase administered every 4 weeks (Q4W) with methotrexate (MTX) compared with every 2 weeks (Q2W) with MTX in participants with uncontrolled refractory gout

Rationale: Compliance with Q2W pegloticase regimen can be burdensome and, therefore, pose a barrier to treatment for some patients who may otherwise benefit from pegloticase. Consequently, there is an unmet need for patients with uncontrolled gout to have access to an effective and well-tolerated therapy, but also have a convenient regimen to potentially improve compliance.

The current trial (FORWARD II) is being conducted to confirm the results with pegloticase 16 mg Q4W observed in the FORWARD trial (HZNP-KRY-408). The FORWARD II trial is a multicenter, randomized, 24-week double-blind trial designed to assess the efficacy, safety and pharmacokinetics (PK) of pegloticase intravenous (IV) infusion of 16 mg Q4W co-administered with MTX, a less-frequent dosing interval, compared with the currently approved dosing regimen (8 mg Q2W co-administered with weekly MTX), followed by a 24-week open-label extension to collect additional safety and efficacy data for pegloticase IV infusion of 16 mg Q4W co-administered with weekly MTX.

Objectives, Endpoints and Estimands:

The overall objective of this trial is to confirm non-inferiority of the efficacy and safety of IV pegloticase 16 mg administered Q4W with oral MTX compared with pegloticase 8 mg administered Q2W with oral MTX in adults with uncontrolled gout.

Objectives	Endpoints
Primary	
To evaluate the effect of pegloticase 16 mg administered Q4W with MTX versus pegloticase 8 mg administered Q2W with MTX, on the response rate during Month 6, as measured by the sustained normalization of serum uric acid (sUA) to < 6 mg/dL for at least 80% of the time	The proportion of Month 6 (Weeks 20, 21, 22, 23 and 24) responders, defined as participants achieving and maintaining sUA < 6 mg/dL for at least 80% of the time during Month 6

Objectives	Endpoints
Secondary	
To evaluate the effect of pegloticase 16 mg Q4W with MTX compared with pegloticase 8 mg Q2W with MTX on tophi resolution at Week 24	The proportion of participants with complete resolution of ≥ 1 tophus (using digital photography) at Week 24 in participants with tophi at Baseline
PK and Immunogenicity	
- Assess the PK of pegloticase - Assess MTX polyglutamate concentrations - Assess the immunogenicity of pegloticase	- Serum concentrations of pegloticase - MTX polyglutamate concentrations - The incidence and titer of anti-polyethylene glycol (PEG) and anti-uricase immunoglobulin G (IgG) antibodies
Safety and Tolerability	
Assess the safety profile, including adverse events (AEs)/serious adverse events (SAEs), laboratory tests and vital signs, of pegloticase 16 mg Q4W with MTX and pegloticase 8 mg Q2W with MTX	- Incidence of AEs/SAEs - Incidence of treatment-emergent adverse events (TEAEs) and SAEs overall and by relationship to investigational product (IP) - Incidence of TEAEs leading to IP discontinuation - Incidence of adverse events of special interest (AESIs): infusion reactions (IRs), anaphylaxis, gout flares, major adverse cardiovascular events (MACE) - Changes in laboratory tests, including hematology and chemistry, from Baseline to each scheduled visit - Changes in vital signs, from Baseline to each scheduled visit

Exploratory objectives and endpoints are listed in Section 3.

Overall Design Synopsis: This is a multicenter, randomized, double-blind, non-inferiority trial followed by an open-label extension.

Brief Summary: This is a Phase 4, multicenter, randomized, 24-week double-blind trial to evaluate the non-inferiority of the efficacy and safety of pegloticase Q4W with MTX versus

pegloticase Q2W with MTX, followed by a 24-week open-label extension of pegloticase Q4W with MTX, in participants with uncontrolled refractory gout.

The trial design includes: 1) a Screening Period (screening should be completed within 5 weeks prior to Week -4); 2) a MTX Run-in Period consisting of 4 weeks of oral MTX; 3) a 24-week double-blind Pegloticase + MTX Period preceded by randomization; 4) a 24-week open-label extension Pegloticase + MTX Period; 5) safety follow-up (phone/email visit) 30 days after the last dose of pegloticase/placebo for pegloticase; and 6) a Follow-up Visit at the investigational site 3 months after the last dose of pegloticase/placebo for pegloticase.

All participants who meet eligibility criteria at Screening will begin MTX 15 mg orally weekly at the Week -4 Visit. All participants will also take folic acid 1 mg orally daily at the beginning of the MTX Run-in Period (Week -4) and continuing until prior to the Week 48 Visit.

Participants will continue to take MTX from Week -4 to Day 1 (the MTX Run-in Period). If a participant does not tolerate MTX 15 mg during the MTX Run-in Period, the participant will be considered a screen failure and will be discontinued from the trial. If a participant does not tolerate the 15 mg MTX dose after the Day 1 Visit, the dose of MTX may be reduced or discontinued based on pre-specified criteria and after discussion with the Sponsor Medical Monitor. The participant should remain in the trial.

All participants who complete the MTX Run-in Period will be randomized in a 1:1 ratio (stratified by presence of tophi based on photographic assessment) to receive the first IV dose of either pegloticase 8 mg or pegloticase 16 mg on Day 1. All subsequent doses and visits will be scheduled based on the Day 1 Visit date.

It is required that, before a participant begins the double-blind Pegloticase + MTX Period, he or she has been taking at least 1 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 et al, 2020](#)). For IR prophylaxis, fexofenadine (180 mg orally) will be taken the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; methylprednisolone (125 mg IV) will be given over an infusion duration of 10 to 30 minutes, immediately prior to each pegloticase infusion. For a participant who is randomized to receive the 16 mg Q4W pegloticase dosing regimen, at the visits when they receive placebo for pegloticase infusion, they will also receive placebo for methylprednisolone pre-infusion, in order to maintain the blind and to reduce unnecessary glucocorticoid exposure.

NOTE: If a participant's hemoglobin A1c (HbA1c) is $> 6.5\%$ at Screening and/or if a participant has a known diagnosis of diabetes mellitus, the pre-infusion IV steroid dose may be reduced (e.g., methylprednisolone 75 mg IV) after consulting with the Horizon Medical Monitor.

During the double-blind Pegloticase + MTX Period, participants will receive IV infusions (pegloticase or placebo) Q2W in order to maintain the blind. Participants randomized to the 16 mg Q4W arm will be administered pegloticase Q4W from Day 1 through the Week 20 Visit and placebo for pegloticase administered Q4W from Week 2 through the Week 22 Visit for a total of 12 infusions. Participants randomized to the 8 mg Q2W arm will be administered pegloticase Q2W from Day 1 through the Week 22 Visit for a total of 12 infusions. During the

open-label extension, all participants will receive pegloticase 16 mg administered IV Q4W from Week 24 through the Week 44 Visit for a total of 6 infusions. Pegloticase and placebo for pegloticase will be administered after all pre-dose trial visit assessments have been completed at each visit. The date and start and stop time of infusion will be recorded. The sUA discontinuation criterion will be applied: participants with a pre-dose sUA level > 6 mg/dL at 2 consecutive trial visits beginning with the Week 2 Visit (not including post-infusion results) will subsequently discontinue pegloticase but remain in the trial to complete the scheduled assessments.

During the double-blind and open-label extension Pegloticase + MTX Periods, participants will be instructed to take MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase/placebo for pegloticase infusion; however, if a participant does not do so, MTX must be taken ≥ 60 minutes prior to each pegloticase/placebo for pegloticase infusion. Three additional weekly doses of MTX will be taken after the last pegloticase/placebo for pegloticase infusion.

After the Week 48 Visit (or End of Pegloticase Infusions Visit [if applicable]), participants 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. Participants will have 30-day (phone/email) and 3-month (at the investigational site) Follow-up Visits for safety.

Samples for measurement of sUA levels, PK analysis of pegloticase, pegloticase immunogenicity, MTX polyglutamate and biomarker analysis will be collected at visits indicated in Section 1.3. Safety assessments, including monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations and monitoring of hematology and blood chemistry, will be performed.

An independent external adjudication committee will review reported events of IR, anaphylaxis and MACE.

An overview of the trial design is presented in Section 1.2 and details of trial activities are provided in Section 1.3.

Individual Participant sUA Discontinuation Criteria: Participants with a pre-infusion sUA level > 6 mg/dL at 2 consecutive trial visits beginning with the Week 2 Visit will discontinue treatment, but continue in the trial, as described in Section 4.2.

No participant in the trial can receive commercially available KRYSTEXXA. Any participant who discontinues pegloticase should be followed to the end of the trial and CANNOT receive commercial KRYSTEXXA. A participant would be required to withdraw from the trial if the plan is to ignore this dosing rule and receive commercial KRYSTEXXA.

Number of Participants: Approximately 240 participants (120 in each treatment group during the 24-week double-blind period) will be enrolled (i.e., receive at least 1 dose of pegloticase on Day 1) at approximately 70 sites in the United States (US).

Trial Arms and Duration: Participants will be randomized in a 1:1 ratio to receive either 16 mg pegloticase Q4W or 8 mg pegloticase Q2W during the 24-week double-blind period. To maintain the blind during the double-blind phase, participants in the 16 mg Q4W arm will receive pegloticase 16 mg administered IV Q4W from Day 1 through the Week 20 Visit and placebo for

pegloticase IV Q4W from Week 2 through Week 22. The total number of infusions in both treatment groups will be 12 during the 24-week double-blind period. The open-label extension will commence at the Week 24 Visit, all participants will receive pegloticase 16 mg administered IV Q4W from Week 24 through the Week 44 Visit for a total of 6 infusions during the 24-week open-label extension. All participants will also receive MTX 15 mg weekly from Week -4 until prior to the Week 48 Visit, inclusive. The maximum total duration of trial participation for each participant is approximately 69 weeks.

Inclusion Criteria:

Eligible participants must meet/provide all of the following criteria:

1. Willing and able to give informed consent
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial
3. Adult men or women ≥ 18 years of age
4. Uncontrolled gout, defined as meeting the following criteria:
 - Hyperuricemia during the Screening Period, defined as $sUA \geq 7$ 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 participant interview, and;
 - Symptoms of gout, including at least 1 of the following:
 - Presence of at least 1 tophus
 - Recurrent flares, defined as 2 or more flares in the 12 months prior to Screening
 - Presence of chronic gouty arthritis
5. Willing to discontinue any oral ULT for at least 7 days prior to MTX dosing at Week -4 and continue not receiving any oral ULT when receiving pegloticase/placebo for pegloticase infusions
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; participants 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/placebo for pegloticase or at least 1 ovulatory cycle after the last dose of MTX (whichever is the longer duration after the last dose of pegloticase/placebo for 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 for at least 3 months after the last dose of MTX.

Exclusion Criteria:

Participants 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 Week -4 Visit
3. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis
4. Current or chronic treatment with systemic immunosuppressive agents, such as MTX, azathioprine or mycophenolate mofetil; prednisone > 10 mg/day or equivalent dose of other corticosteroid on a chronic basis (3 months or longer)
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 (G6PD) deficiency (quantitative test at the Screening Visit centrally or locally)
10. Chronic renal impairment, defined as estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m² 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 Week -4
12. Uncontrolled diabetes mellitus
13. 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
14. Prior treatment with pegloticase, another recombinant uricase (rasburicase) or concomitant therapy with a PEG-conjugated drug
15. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product
16. Contraindication to MTX treatment or MTX treatment considered inappropriate
17. Known intolerance to MTX
18. Unable to tolerate MTX 15 mg orally during the MTX Run-in Period
19. 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
20. Liver transaminase levels (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) > upper limit of normal (ULN) or albumin < the lower limit of normal (LLN) at the Screening Visit
21. Chronic liver disease
22. White blood cell count < 4,000/ μ L, hematocrit < 32% or platelet count < 75,000/ μ L
23. HbA1c > 8%
24. Currently receiving systemic or radiologic treatment for ongoing cancer

25. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix
26. Diagnosis of osteomyelitis
27. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome
28. 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 participant or interfere with the participant's ability to comply with the protocol requirements or complete the trial
29. Alcohol use in excess of 3 alcoholic beverages per week
30. A known intolerance to all protocol-standard gout flare prophylaxis regimens (i.e., participant must be able to tolerate at least 1 of the following: colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤ 10 mg/day)
31. Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest X-ray may be performed during Screening.

Statistical Analyses:

Sample Size Determination: A sample size of approximately 240 (120 participants per treatment group) is planned to demonstrate the non-inferiority of the pegloticase 16 mg Q4W + MTX co-administration group compared with the pegloticase 8 mg Q2W + MTX co-administration group (i.e., the active-controlled group in this trial). With a non-inferiority margin set at 20%, this sample size achieves 90% power, assuming a responder rate of 65% in both groups at the 1-sided Type I error rate of 0.025.

Analysis Sets:

- Full Analysis Set (FAS): all participants who receive at least 1 dose of pegloticase. Efficacy analyses will be based on the FAS.
- MTX Analysis Set (MAS): all participants who receive at least 1 dose of MTX.
- Safety Analysis Set (SAS): all participants who receive at least 1 dose of pegloticase. Safety analyses will be performed on the SAS.
- PK Analysis Set: all participants who receive at least 1 dose of pegloticase and have at least 1 quantifiable serum PK observation post-first dose.

Statistical Analysis Methods:Efficacy

The primary analysis will be conducted on the FAS. The primary efficacy endpoint is the proportion of responders during Month 6. A responder is defined as a participant for whom the proportion of time that the sUA-time curve is < 6 mg/dL during the analysis interval is at least 80%. The proportion of time that the sUA level is below 6 mg/dL is defined as the ratio of the time during which the sUA level remains below 6 mg/dL (using linear interpolation, if necessary) during the entire Month 6 interval. A participant will be declared a non-responder if

the participant had an sUA level > 6 mg/dL at 2 consecutive trial visits prior to or during Month 6 beginning with the Week 2 Visit.

The primary endpoint will be analyzed using g-computation to estimate the covariate adjusted unconditional treatment effect with 95% CI (Ye et al., 2023). Logistic regression will be used as the working model in the g-computation procedure with treatment and covariates (including but not limited to) for tophi presence (present, not present), age, and baseline eGFR. The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups is less than the non-inferiority margin of 20%.

The proportion of participants with resolution of ≥ 1 tophus (100% decrease in the area of at least 1 tophus) at Week 24 will be analyzed using the same g-computation procedure used for the primary endpoint to estimate the covariate adjusted unconditional treatment effect with 95% CI. Logistic regression will be used as the working model in the g-computation procedure with treatment and covariates (including but not limited to) for age, and baseline eGFR. The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups is less than the non-inferiority margin of 15%.

Safety and Tolerability Endpoints

The incidences of TEAEs, including SAEs, TEAEs leading to discontinuation of IP (MTX or pegloticase) and TEAEs of special interest, will be summarized.

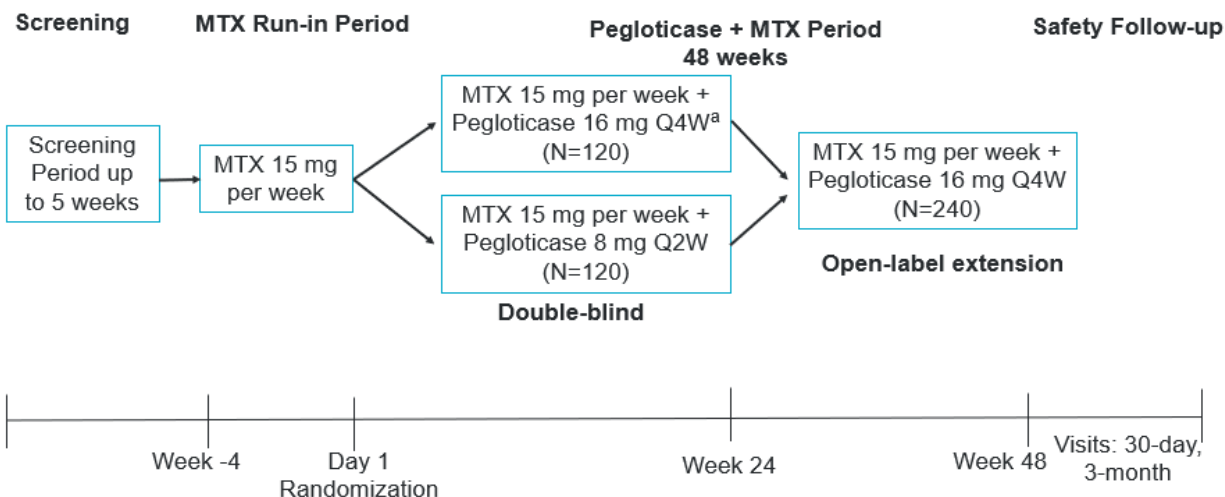
Other safety parameters, including but not limited to, laboratory assessments, vital signs and electrocardiogram (ECG) will also be summarized using the SAS.

The primary analysis of efficacy is planned when all participants complete Week 24, the timepoint for the primary efficacy endpoint, in the double-blind Pegloticase + MTX Period or terminate early from the trial. A final analysis will be performed after all participants have completed the trial.

Additionally, safety data will be reviewed periodically throughout the trial. Safety reviews prior to the primary analysis will be reviewed in a blinded manner.

Adjudication Committee: An independent external adjudication committee will review reported events of IR, anaphylaxis, and MACE.

1.2 Schema



MTX = methotrexate; Q2W = every 2 weeks; Q4W = every 4 weeks

- In order to maintain the blind during the double-blind portion of the trial, participants in the 16 mg Q4W treatment group will receive pegloticase 16 mg administered IV Q4W from Day 1 through the Week 20 Visit and placebo for pegloticase IV Q4W from Week 2 through Week 22

1.3 Schedule of Activities (SoA)

	Screening ^a	MTX Run-in Period ^b		Double-blind Pegloticase + MTX Period ^c (Day 1 through Week 23)														
		Screening Visit	(-4 wks ±3 d)	(-2 wks ±3 d)	*Day 1	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 8 (±3 d)	Wk 10 (±3 d)	Wk 12 (±3 d)	Wk 14 (±3 d)	Wk 16 (±3 d)	Wk 18 (±3 d)	Wk 20 (±3 d)	Wk 21 (±3 d)	Wk 22 (±3 d)	Wk 23 (±3 d)
Trial Procedure/ Assessment**				Inf:1	Inf:2	Inf:3	Inf:4	Inf:5	Inf:6	Inf:7	Inf:8	Inf:9	Inf:10	Inf:11		Inf:12		
Informed consent	X																	
Demographic data	X																	
Inclusion/exclusion criteria	X	X	X	X														
Medical/surgical/substance use history ^c	X																	
Medication use history ^f	X																	
Chest X-ray ^g	X																	
Physical examination ^h	X	X		X		X		X		X		X		X				
Vital signs, height and weight ⁱ	X	X		X	X	X	X	X	X	X	X	X	X	X		X		
ECG ^j	X																	
Document gout flares and intensity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MTX/oral dosing calendar		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MTX/oral dispensed ^l		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MTX/oral dosing ^l		Once weekly from Week -4 until prior to the Week 48 Visit, inclusive																
Gout flare prophylaxis Rxs filled ^m		Rxs filled as needed																
Folic acid Rx filled ⁿ		Rxs filled as needed																
MTX/oral compliance/reconciliation ^l		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IR prophylaxis Rx filled ^o				X	X	X	X	X	X	X	X	X	X	X		X		
IR prophylaxis compliance (Yes/No)				X	X	X	X	X	X	X	X	X	X	X		X		
Folic acid compliance (Yes/No)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gout flare prophylaxis compliance (Yes/No)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening ^a	MTX Run-in Period ^b		Double-blind Pegloticase + MTX Period ^c (Day 1 through Week 23)														
		Screening Visit	(-4 wks ±3 d)	(-2 wks ±3 d)	*Day 1	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 8 (±3 d)	Wk 10 (±3 d)	Wk 12 (±3 d)	Wk 14 (±3 d)	Wk 16 (±3 d)	Wk 18 (±3 d)	Wk 20 (±3 d)	Wk 21 (±3 d)	Wk 22 (±3 d)	Wk 23 (±3 d)
Trial Procedure/ Assessment**				Inf:1	Inf:2	Inf:3	Inf:4	Inf:5	Inf:6	Inf:7	Inf:8	Inf:9	Inf:10	Inf:11		Inf:12		
Double-blind infusion (pegloticase/placebo for pegloticase)				X	X	X	X	X	X	X	X	X	X	X	X		X	
Pegloticase PK sampling ^p				X	X	X		X		X				X		X		
Plasma and serum samples for biomarker analysis ^q	X			X	X	X		X		X								
Urine sample for biomarker analysis ^q	X			X	X	X		X		X								
Pre-infusion MTX polyglutamate sampling				X						X								
sUA ^r	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				
Clinical chemistry sample ^s	X	X	X	X	X	X		X		X		X		X				
HbA1c ^s	X									X								
Spot urine				X							X							
hs-CRP				X							X							
Antibody sample ^u				X		X		X		X				X				
G6PD test	X																	
Pregnancy test ^v	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Adverse event assessment ^w	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Open-label Extension Pegloticase + MTX Period ^c (Week 24 through Week 48)														Safety Follow-up	
	Wk 24 (±3 d)	Wk 26 (±3 d)	Wk 28 (±3 d)	Wk 30 (±3 d)	Wk 32 (±3 d)	Wk 34 (±3 d)	Wk 36 (±3 d)	Wk 38 (±3 d)	Wk 40 (±3 d)	Wk 42 (±3 d)	Wk 44 (±3 d)	Wk 46 (±3 d)	End of Pegloticase Infusions Visit ^d (if applicable)	EOT/ ET/ Wk 48 (±3 d)	30 d (phone/ email)	3 M
Trial Procedure/ Assessment**	Inf:13		Inf:14		Inf:15		Inf:16		Inf:17		Inf:18					
Physical examination ^h	X						X						X	X		X

	Open-label Extension Pegloticase + MTX Period ^c (Week 24 through Week 48)														Safety Follow-up	
	Wk 24 (±3 d)	Wk 26 (±3 d)	Wk 28 (±3 d)	Wk 30 (±3 d)	Wk 32 (±3 d)	Wk 34 (±3 d)	Wk 36 (±3 d)	Wk 38 (±3 d)	Wk 40 (±3 d)	Wk 42 (±3 d)	Wk 44 (±3 d)	Wk 46 (±3 d)	End of Pegloticase Infusions Visit ^d (if applicable)	EOT/ ET/ Wk 48 (±3 d)	30 d (phone/ email)	3 M
Trial Procedure/ Assessment**	Inf:13		Inf:14		Inf:15		Inf:16		Inf:17		Inf:18					
Vital signs, height and weight ⁱ	X		X		X		X		X		X		X	X		X
Document gout flares and intensity	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
MTX/oral dosing calendar	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MTX/oral dispensed ^l	X	X	X	X	X	X	X	X	X	X	X	X				
MTX/oral dosing ^l	Once weekly from Week -4 until prior to the Week 48 Visit, inclusive															
Gout flare prophylaxis Rxs filled ^m	Rxs filled as needed															
Folic acid Rx filled ⁿ	Rxs filled as needed															
MTX/oral compliance/reconciliation ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IR prophylaxis Rx filled ^o	X		X		X		X		X		X					
IR prophylaxis compliance (Yes/No)	X		X		X		X		X		X					
Folic acid compliance (Yes/No)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Gout flare prophylaxis compliance (Yes/No)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Open-label infusion pegloticase	X		X		X		X		X		X					
Pegloticase PK sampling ^p	X						X						X	X		

	Open-label Extension Pegloticase + MTX Period ^c (Week 24 through Week 48)														Safety Follow-up	
	Wk 24 (±3 d)	Wk 26 (±3 d)	Wk 28 (±3 d)	Wk 30 (±3 d)	Wk 32 (±3 d)	Wk 34 (±3 d)	Wk 36 (±3 d)	Wk 38 (±3 d)	Wk 40 (±3 d)	Wk 42 (±3 d)	Wk 44 (±3 d)	Wk 46 (±3 d)	End of Pegloticase Infusions Visit ^d (if applicable)	EOT/ ET/ Wk 48 (±3 d)	30 d (phone/ email)	3 M
Trial Procedure/ Assessment**	Inf:13		Inf:14		Inf:15		Inf:16		Inf:17		Inf:18					
Pre-infusion MTX polyglutamate sampling	X						X									
Plasma and serum samples for biomarker analysis ^a	X													X		X
Urine sample for biomarker analysis ^a	X													X		X
sUA ^r	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology sample	X						X						X	X		X
Clinical chemistry sample ^s	X						X						X	X		X
HbA1c ^s	X						X									
Spot urine	X				X								X	X		
hs-CRP	X				X							X		X		
Antibody sample ^u	X						X						X	X		
Pregnancy test ^v	X		X		X		X		X		X		X	X	X	
Partner pregnancy																X ^z
Adverse event assessment ^w	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

AE = adverse event; AESI = adverse event of special interest; d = day(s); ECG = electrocardiogram; eCRF = electronic case report form; EOT = End-of-Trial; ET = Early Termination; G6PD = glucose-6-phosphate dehydrogenase; [REDACTED]; HbA1c = hemoglobin A1c; HEENT = head, ears, eyes, nose, throat; hs-CRP = high-sensitivity C-reactive protein; ICF = informed consent form; IgG = immunoglobulin G; Inf = infusion; IR = infusion reaction; IV = intravenous; MTX = methotrexate; M = months; PEG = polyethylene glycol; PK = pharmacokinetic; Q4W = every 4 weeks; Rx = prescription; sUA = serum uric acid; [REDACTED] wk(s) = week(s)

*All time points after Day 1 are relative to Day 1.

**All assessments will be completed prior to the pegloticase/placebo for pegloticase infusions, with the exception of the following assessments which are also required to be conducted post-infusion; post infusion sUA, post-infusion PK, post-infusion vital signs.

a. The Screening Visit can occur any time within 5 weeks prior to the first dose of MTX at Week -4.

b. During the MTX Run-in Period (Week -4 until the Day 1 Visit), all participants will take MTX 15 mg orally weekly. If a participant does not tolerate MTX 15 mg during the MTX Run-in Period, the participant will be considered a screen failure and will be discontinued from the trial. If a participant does not tolerate the 15 mg MTX dose after the

Day 1 Visit, MTX may be dose-reduced or discontinued based on pre-specified criteria and after discussion with the Sponsor Medical Monitor. The participant should remain in the trial.

- c. 24-week double-blind Pegloticase + MTX Period (Day 1 through Week 23) and 24-week open-label extension Pegloticase + MTX Period (Week 24 through Week 48).
- d. Participants who end pegloticase early (i.e., prior to Week 44) due to the sUA discontinuation criterion or other reasons, are to complete the End of Pegloticase Infusions Visit within 2 weeks of the last infusion. Participants are to remain in the trial and continue with trial procedures without infusion. All participants, including those who do not discontinue pegloticase early, will also complete all regularly scheduled Follow-up Visits, including the Week 48/EOT/ET Visit, the 30-day Post-treatment Follow-up email/phone call and the 3-month Safety Follow-up Visit.
- e. The Investigator or designee will collect a complete gout history and other relevant medical/surgical/substance use history.
- f. 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.
- g. Participants who 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.
- h. A complete physical examination will be performed at the Screening Visit, including assessment of HEENT, heart, lungs, abdomen, skin, extremities, neurological status, and musculoskeletal. A targeted physical examination per Investigator judgement will be conducted at Week -4, prior to administration of pegloticase on Day 1 and at Weeks 4, 8, 12, 16, 20, 24, 36, and at the End of Pegloticase Infusions (if applicable), Week 48/EOT/ET and 3-month Safety Follow-up Visits; at a minimum this should include examination of the heart, lungs and abdomen. Clinically significant findings from the targeted physical examinations will be recorded as AEs.
- i. Routine vital signs, including blood pressure, respiratory rate, temperature and heart rate, will be measured at Screening, Week -4, Day 1, each subsequent infusion visit, and at the End of Pegloticase Infusions (if applicable), Week 48/EOT/ET and 3-month Safety Follow-up Visits. During the double-blind and open-label extension Pegloticase + MTX Periods trial visits, vitals should be taken before the pegloticase/placebo for pegloticase infusion and any time after the end of the infusion, but prior to participant's discharge/release from the site. Height will be recorded at the Screening Visit only. Weight should be measured pre-infusion at all visits that vital signs are collected.
- j. 12-lead ECG should be completed during Screening. The ECG is read at the site. When possible, a 12-lead ECG will also be performed at the time an AESI of IR, anaphylaxis or cardiovascular event is suspected.

- l. MTX will be dispensed and brought back to the site by the participant to check compliance until the ET/EOT Visit. MTX should be taken 1 to 3 days prior to each pegloticase/placebo for pegloticase infusion; however, if a participant does not do so, MTX must be taken ≥ 60 minutes prior to each pegloticase/placebo for pegloticase infusion.
- m. It is required that, before a participant begins the double-blind Pegloticase + MTX Period, he or she has been taking at least 1 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 et al, 2020](#)).
- n. Participants will take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the End of Pegloticase Infusions Visit (if applicable) or the EOT/ET.
- o. IR prophylaxis includes fexofenadine (180 mg orally) administered the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) administered on the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 and 30 minutes, immediately prior to each pegloticase infusion. Participants randomized to the Q4W regimen will receive placebo for methylprednisolone before the placebo for pegloticase infusion starting at Week 2.
- p. For all participants, serum samples for PK analysis will be collected after the end of infusion on Day 1 (prior to discharge); prior to the pegloticase/placebo for pegloticase infusion and after the end of infusion (prior to discharge) at Weeks 2, 4, 8, 12, 20, 22, 24 and 36. Additional PK samples will be collected at the following non-infusion visits: End of Pegloticase Infusions Visit (if applicable) and Week 48/EOT/ET Visit.

- q. Plasma, serum and urine samples for biomarker analysis will be collected at Screening, prior to the pegloticase/placebo for pegloticase infusion at Day 1 and Weeks 2, 4, 8, 12, 24, and at any time during Week 48 and 3M FU visits. For subjects where no Day 1 pre-infusion samples were collected, biomarker samples will not be collected at the subsequent visits.
- r. Serum samples for measurement of sUA levels will be collected and sent to the central laboratory at the Screening Visit, the Week -4 Visit (prior to the first dose of MTX) and the Week -2 Visit during the MTX Run-in Period. - On all infusion visit dates starting at Day 1, a pre-infusion and post-infusion sUA will be collected to be shipped to the Central Laboratory. Additional serum samples for sUA levels will be collected at non-infusion visits at Weeks 21, 23, 26, 30, 34, 38, 42, 46, the End of Pegloticase Infusions Visit (if applicable), the Week 48/EOT/ET Visit and 3-month Follow-up Visit and sent to the Central Laboratory. For all infusion visits beginning at Week 2 during the double-blind and open-label extension Pegloticase + MTX Periods, 1 sUA sample will be collected locally within 48 hours PRIOR to each infusion visit until the Week 44 Visit for determination by a local laboratory if the sUA discontinuation criterion has been met. See the Laboratory Manual for instructions.
- s. HbA1c testing must be performed at Screening for all participants. If HbA1c > 6.5% and/or if participant has known diagnosis of diabetes mellitus, additional measures will be taken during the trial including HbA1c every 3 months. Additionally, participants that are diabetic or with elevated HbA1c's at Screening will be assessed for elevated blood glucose and symptoms of hyperglycemia prior to methylprednisolone infusion and after pegloticase infusion via finger prick test. Participants with clinically significant hyperglycemia (as determined by Investigators and/or Sponsor) or preexisting diabetes must be under appropriate glycemic control before and while receiving pegloticase. Additional information including relevant medical history and HbA1c level must be collected for participants with clinically significant hyperglycemia.
- t. This superscript intentionally left blank.
- u. Serum samples for evaluation of anti-PEG and antiuricase immunoglobulin G (IgG) antibodies will be collected prior to the pegloticase infusion on Day 1, Weeks 4, 8, 12, 20, 24, 36 and additional samples at the non-infusion End of Pegloticase Infusions Visit (if applicable) and Week 48/EOT/ET Visit. In the event of an AE suspected to be an IR, a serum sample will be collected at that time or at the subsequent visit for evaluation of pegloticase antibodies.
- v. For women of childbearing potential, a serum pregnancy test (for the central laboratory) will be performed at the Screening Visit. A local urine pregnancy test will be performed prior to MTX dosing during the MTX Run-in Period and prior to each infusion at the infusion visits, at the End of Pegloticase Infusions Visit (if applicable) and at the Week 48/EOT/ET Visit. Participants who receive at least 1 dose of MTX and are females of childbearing potential will receive a safety follow-up phone call/email approximately 4 weeks/30 days after the last dose of MTX to verify at least 1 ovulatory cycle has occurred after the last dose of MTX. If the participant has not ovulated, a urine pregnancy test will be performed.
- w. Adverse events will be collected from the signing of the informed consent form (ICF) until the 3-month Safety Follow-up Visit. For each AE, the Investigator will be asked to record if the event was possibly an IR or anaphylaxis and if so, will be prompted to complete additional eCRFs.
- x. Participants who are non-vasectomized males will be asked 3 months after MTX discontinuation regarding partner pregnancy. This will occur at the scheduled 3-month Safety Follow-up Visit or by a separate phone/email visit (if MTX discontinuation does not align with trial discontinuation).

2 INTRODUCTION

2.1 Background

Gout affects approximately 4% of the United States (US) 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 US experience chronic symptoms of gout, sometimes referred to as chronic refractory gout, despite trials of oral urate-lowering therapy (ULT). Chronic refractory gout is characterized by ongoing symptoms of active disease and a failure to control/maintain serum uric acid (sUA) < 6 mg/dL with conventional xanthine oxidase inhibitors (i.e., allopurinol and febuxostat) and uricosuric agents (i.e., probenecid) ([AAC Briefing Document, 2009](#); [Brook et al, 2010](#); [Wertheimer et al, 2010](#); [Khanna et al, 2016](#)). These patients often have significant, disabling urate deposits in soft tissues and bone known as tophi.

Pegloticase, a recombinant modified mammalian urate oxidase (uricase), is approved for the treatment of adult patients with chronic gout refractory to conventional therapy. Pegloticase is efficacious in reducing sUA levels and improving clinical signs and symptoms of gout, while also eliminating tophi in patients who currently have no other therapeutic options. The efficacy and safety of intravenous (IV) pegloticase 8 mg every 2 weeks (Q2W) as monotherapy were previously established by replicate 6-month, Phase 3 trials (C0405 and C0406), which were the basis of initial approval of pegloticase as KRYSTEXXA in 2010. Subsequently, the efficacy and safety of co-administering pegloticase with methotrexate (MTX) were demonstrated in a 52-week, randomized, controlled trial, MIRROR-RCT (HZNP-KRY-202), which was the basis for a supplemental Biologics License Application (sBLA) approval in 2022.

The currently approved dose regimen of KRYSTEXXA is 8 mg Q2W given as an IV infusion, co-administered with weekly MTX 15 mg orally. KRYSTEXXA alone may be used in patients for whom MTX is contraindicated or not clinically appropriate. The currently approved 8 mg dosage regimen requires IV infusion over no less than 120 minutes, with re-administration Q2W to achieve optimal therapeutic outcomes, prevent elevations in sUA levels and reduce tophus burden.

Additional background concerning KRYSTEXXA can be found in the current versions of the Pegloticase (KRYSTEXXA) Investigator's Brochure and Food and Drug Administration (FDA)-approved KRYSTEXXA full prescribing information ([KRYSTEXXA Prescribing Information, 2022](#)). Additional background concerning MTX can be found in the current version of the approved MTX full prescribing information.

2.2 Trial Rationale

Compliance with Q2W pegloticase regimen can be burdensome and, therefore, pose a barrier to treatment for some patients who may otherwise benefit from pegloticase. Consequently, there is an unmet need for patients with uncontrolled gout to have access to an effective and well-tolerated therapy, but also have a convenient regimen to potentially improve compliance.

The current trial (FORWARD II) is being conducted to confirm the results with pegloticase 16 mg every 4 weeks (Q4W) observed in the FORWARD trial (HZNP-KRY-408). The FORWARD II trial is a multicenter, randomized, 24-week double-blind trial designed to assess the efficacy, safety and pharmacokinetics (PK) of pegloticase IV infusion of 16 mg Q4W co-administered with MTX, a less-frequent dosing interval, compared with the currently approved dosing regimen (8 mg Q2W co-administered with weekly MTX), followed by a 24-week open-label extension to collect additional safety and efficacy data for pegloticase IV infusion of 16 mg Q4W co-administered with weekly MTX.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment for 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

Participants 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 participants receive prophylactic treatment to reduce the risk of acute gout flares, unless medically contraindicated or not tolerated, as noted in the pegloticase prescribing information. Participants will begin at least 1 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 pegloticase treatment per American College of Rheumatology guidelines ([Fitzgerald et al, 2020](#)).

Since IRs can occur, all participants will receive pre-treatment prophylaxis consisting of an antihistamine, acetaminophen and a corticosteroid prior to each infusion of pegloticase. To standardize this regimen, participants 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 and 30 minutes, immediately prior to each infusion. Refer to Section 6.1.5 for further details.

In the replicate Phase 3 clinical trials with pegloticase 8 mg that were the basis of the original approval, a pegloticase 8 mg Q4W dosing interval was investigated without immunomodulation or an sUA discontinuation criterion. A pegloticase 8 mg Q4W regimen is not approved in the current prescribing information because it led to increased IRs compared to a pegloticase 8 mg Q2W dosing regimen, suggesting that an 8 mg dose is too low for a Q4W regimen. In addition, the IRs appeared to be driven in part by development of anti-drug antibody (ADA) response to pegloticase. Based on data from MIRROR-RCT and the subsequent sBLA approval on 07 July 2022 (BLA 125293/S-104), pre-treatment and co-administration with MTX reduces the immunogenic potential of pegloticase, thereby lowering the incidence of IRs. Therefore,

pegloticase at a dose of 16 mg Q4W is being co-administered with MTX to reduce the immunogenic potential of pegloticase and potentially improve the rate of response to pegloticase when administered Q4W.

The risk of anaphylaxis and IRs is higher in participants whose sUA level increases to > 6 mg/dL. Beginning with Week 2, a participant with an sUA level > 6 mg/dL at 2 consecutive trial visits will be classified as a non-responder. These participants will discontinue pegloticase and remain in the trial but cannot receive commercially available KRYSTEXXA.

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

2.3.2 Risk Assessment for MTX

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

Adverse events (AEs) that may be experienced by participants 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 and during and for a minimum of 3 months after MTX therapy for the non-vasectomized male. For females of childbearing potential, pregnancy should be avoided during and for at least 1 ovulatory cycle after MTX therapy.

Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests and, if deemed necessary by the Investigator, 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.

2.3.3 Benefit Assessment

Pegloticase (KRYSTEXXA) is approved for the treatment of adult patients with chronic gout refractory to conventional therapy. Pegloticase reduces sUA levels and improves clinical signs and symptoms of gout, while also eliminating tophi in patients who currently have no other therapeutic options. The efficacy and safety of IV pegloticase 8 mg Q2W as monotherapy were previously established by replicate 6-month, Phase 3 trials (C0405 and C0406), which were the basis of initial approval of pegloticase as KRYSTEXXA in 2010. Subsequently, the efficacy and safety of co-administering pegloticase with MTX were demonstrated in a 52-week, randomized, controlled trial, MIRROR-RCT, which was the basis for an sBLA approval.

2.3.4 Overall Benefit Risk Conclusion

Pegloticase (KRYSTEXXA) is currently the only approved therapy for uncontrolled gout, but its efficacy is limited by ADA formation, which can lead to adverse immune consequences, including IRs and anaphylaxis. Loss of therapeutic response to pegloticase due to ADA formation is mitigated by pre-treatment with and concomitant use of MTX with pegloticase. In addition to the sUA-lowering effect, clinically important improvements with combination therapy of pegloticase and MTX have been observed with respect to tophus resolution and



Pegloticase + MTX was generally safe and well tolerated in a population with uncontrolled gout. The safety profile was generally similar to that observed with pegloticase monotherapy in the previous Phase 3 registrational trials, with the exception of IRs, which were markedly reduced with the co-administration of MTX.

Use of the sUA discontinuation criterion (i.e., discontinuation of pegloticase if sUA is > 6 mg/dL at 2 consecutive trial visits beginning with the Week 2 Visit [excluding post-infusion values]) and standardized pre-infusion treatment are important to minimize the incidence of IRs/anaphylaxis and will be utilized in this trial.

In conclusion, the benefit-to-risk ratio of concomitant use of MTX with pegloticase is highly favorable for patients with uncontrolled gout refractory to oral ULT, and in whom an immunomodulator is clinically appropriate.

3 OBJECTIVES AND ENDPOINTS

The overall objective of this trial is to confirm non-inferiority of the efficacy and safety of IV pegloticase 16 mg administered Q4W with oral MTX compared with pegloticase 8 mg administered Q2W with oral MTX in adults with uncontrolled gout.

Objectives	Endpoints
Primary	
To evaluate the effect of pegloticase 16 mg administered Q4W with MTX versus pegloticase 8 mg administered Q2W with MTX, on the response rate during Month 6, as measured by the sustained normalization of sUA to < 6 mg/dL for at least 80% of the time	The proportion of Month 6 (Weeks 20, 21, 22, 23 and 24) responders, defined as participants achieving and maintaining sUA < 6 mg/dL for at least 80% of the time during Month 6
Secondary	
To evaluate the effect of pegloticase 16 mg Q4W with MTX compared with pegloticase 8 mg Q2W with MTX on tophi resolution at Week 24	The proportion of participants with complete resolution of ≥ 1 tophus (using digital photography) at Week 24 in participants with tophi at Baseline
Exploratory	

Objectives	Endpoints
PK and Immunogenicity	
- Assess the PK of pegloticase - Assess MTX polyglutamate concentrations	- Serum concentrations of pegloticase - MTX polyglutamate concentrations - The incidence and titer of anti-polyethylene glycol (PEG) and

Objectives	Endpoints
Assess the immunogenicity of pegloticase	anti-uricase immunoglobulin G (IgG) antibodies
Safety and Tolerability	
Assess the safety profile, including AEs/serious adverse events (SAEs), laboratory tests and vital signs, of pegloticase 16 mg Q4W with MTX and pegloticase 8 mg Q2W with MTX	- Incidence of AEs/SAEs - Incidence of treatment-emergent adverse events (TEAEs) and SAEs overall and by relationship to investigational product (IP) - Incidence of TEAEs leading to IP discontinuation - Incidence of adverse events of special interest (AESIs): IRs, anaphylaxis, gout flares, major adverse cardiovascular events (MACE) - Changes in laboratory tests, including hematology and chemistry, from Baseline to each scheduled visit - Changes in vital signs, from Baseline to each scheduled visit

4 TRIAL DESIGN

4.1 Overall Design

This is a Phase 4, multicenter, randomized, 24-week double-blind trial to evaluate the non-inferiority of the efficacy and safety of pegloticase Q4W with MTX versus pegloticase Q2W with MTX, followed by a 24-week open-label extension of pegloticase Q4W with MTX, in participants with uncontrolled refractory gout.

The trial design includes: 1) a Screening Period (screening should be completed within 5 weeks prior to Week -4); 2) a MTX Run-in Period consisting of 4 weeks of oral MTX; 3) a 24-week double-blind Pegloticase + MTX Period preceded by randomization; 4) a 24-week open-label extension Pegloticase + MTX Period; 5) safety follow-up (phone/email visit) 30 days after the last dose of pegloticase/placebo for pegloticase; and 6) a Follow-up Visit at the investigational site 3 months after the last dose of pegloticase/placebo for pegloticase.

All participants who meet eligibility criteria at Screening will begin MTX 15 mg orally weekly at the Week -4 Visit. All participants will also take folic acid 1 mg orally daily at the beginning of the MTX Run-in Period (Week -4) and continuing until prior to the Week 48 Visit.

Participants will continue to take MTX from Week -4 to Day 1 (the MTX Run-in Period). If a participant does not tolerate MTX 15 mg during the MTX Run-in Period, the participant will be considered a screen failure and will be discontinued from the trial. If a participant does not tolerate the 15 mg MTX dose after the Day 1 Visit, the dose of MTX may be reduced or discontinued based on pre-specified criteria and after discussion with the Sponsor Medical Monitor. The participant should remain in the trial.

All participants who complete the MTX Run-in Period will be randomized in a 1:1 ratio (stratified by presence of tophi based on photographic assessment) to receive the first IV dose of either pegloticase 8 mg or pegloticase 16 mg on Day 1. All subsequent doses and visits will be scheduled based on the Day 1 Visit date.

It is required that, before a participant begins the double-blind Pegloticase + MTX Period, he or she has been taking at least 1 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 et al, 2020](#)). For IR prophylaxis, fexofenadine (180 mg orally) will be taken the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; methylprednisolone (125 mg IV) will be given over an infusion duration of 10 to 30 minutes, immediately prior to each pegloticase infusion. For a participant who is randomized to receive the 16 mg Q4W pegloticase dosing regimen, at the visits when they receive placebo for pegloticase infusion, they will also receive placebo for methylprednisolone pre-infusion, in order to maintain the blind and to reduce unnecessary glucocorticoid exposure.

NOTE: If a participant's hemoglobin A1c (HbA1c) is $> 6.5\%$ at Screening and/or if a participant has a known diagnosis of diabetes mellitus, the pre-infusion IV steroid dose may be reduced (e.g., methylprednisolone 75 mg IV) after consulting with the Horizon Medical Monitor.

During the double-blind Pegloticase + MTX Period, participants will receive IV infusions (pegloticase or placebo) Q2W in order to maintain the blind. Participants randomized to the 16 mg Q4W arm will be administered pegloticase Q4W from Day 1 through the Week 20 Visit and placebo for pegloticase administered Q4W from Week 2 through the Week 22 Visit for a total of 12 infusions. Participants randomized to the 8 mg Q2W arm will be administered pegloticase Q2W from Day 1 through the Week 22 Visit for a total of 12 infusions. During the open-label extension, all participants will receive pegloticase 16 mg administered IV Q4W from Week 24 through the Week 44 Visit for a total of 6 infusions. Pegloticase and placebo for pegloticase will be administered after all pre-dose trial visit assessments have been completed at each visit. The date and start and stop time of infusion will be recorded. The sUA discontinuation criterion will be applied: participants with a pre-dose sUA level > 6 mg/dL at 2 consecutive trial visits beginning with the Week 2 Visit (not including post-infusion results) will subsequently discontinue pegloticase but remain in the trial to complete the scheduled assessments.

During the double-blind and open-label extension Pegloticase + MTX Periods, participants will be instructed to take MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase/placebo for pegloticase infusion; however, if a participant does not do so, MTX must be taken ≥ 60 minutes prior to each pegloticase/placebo for pegloticase infusion. Three additional weekly doses of MTX will be taken after the last pegloticase/placebo for pegloticase infusion.

After the Week 48 Visit (or End of Pegloticase Infusions Visit [if applicable]), participants should resume regular care for gout per the judgment of the treating physician, including resumption of ULT upon pegloticase/placebo for pegloticase discontinuation, if appropriate. Participants will have 30-day (phone/email) and 3-month (at the investigational site) Follow-up Visits for safety.

Samples for measurement of sUA levels, PK analysis of pegloticase, pegloticase immunogenicity and MTX polyglutamate analysis will be collected at visits indicated in Section 1.3. Safety assessments, including monitoring and recording of all AEs, whether or not drug-related, measurement of vital signs, physical examinations and monitoring of hematology and blood chemistry, will be performed.

An independent external adjudication committee will review reported events of IR, anaphylaxis and MACE.

An overview of the trial design is presented in Section 1.2 and details of trial activities are provided in Section 1.3.

The maximum total duration of trial participation for each participant is approximately 69 weeks.

4.2 Individual Participant sUA Discontinuation Criteria

Participants with a pre-infusion sUA level > 6 mg/dL at 2 consecutive trial visits beginning with the Week 2 Visit will discontinue treatment but continue in the trial.

No participant in the trial can receive commercially available KRYSTEXXA. Any participant who discontinues pegloticase should be followed to the end of the trial and CANNOT receive commercial KRYSTEXXA. A participant would be required to withdraw from the trial if the plan is to ignore this dosing rule and receive commercial KRYSTEXXA.

4.3 Scientific Rationale for Trial Design

This is a randomized, 24-week double-blind trial to confirm non-inferiority of the efficacy and safety of the 16 mg Q4W regimen co-administered with weekly MTX compared with the currently approved dosing regimen (pegloticase 8 mg Q2W with oral MTX), followed by a 24-week open-label extension of pegloticase Q4W with MTX in adults with uncontrolled gout.

Since this trial is designed to evaluate the efficacy, safety and tolerability of pegloticase Q4W administered with MTX, the design is similar to that of MIRROR-RCT (HZNP-KRY-202), which was the basis of sBLA approval for co-administration with MTX. The primary efficacy endpoint is the same as that used in MIRROR-RCT. In addition, AESIs—IRs, anaphylaxis and MACE—will be independently adjudicated against pre-defined criteria (consistent with those used in MIRROR-RCT) to assess incidence rates of these AEs during pegloticase Q4W dosing. The same prospective sUA discontinuation criterion employed in MIRROR-RCT (i.e., sUA level > 6 mg/dL at 2 consecutive trial visits beginning with the Week 2 Visit [excluding post-infusion values]) will be used to reduce IR and anaphylaxis risk.

4.4 Justification for Dose

Emerging data from the ongoing FORWARD trial demonstrate the benefit of Q4W dosing of pegloticase co-administered with weekly oral doses of MTX in decreasing ADAs to pegloticase and increasing sUA response rates, thus supporting further clinical development. A pegloticase dose of 16 mg Q4W was selected for Trial HZNP-KRY-409 based on preliminary results from the FORWARD trial.

Preliminary efficacy results are similar in the 2 cohorts (16 mg Q4W and 30 mg Q4W) in the FORWARD trial. The Month 3 sUA responder rate is 84.0% in the 16 mg Q4W group and 76.9% in the 30 mg Q4W group. The Month 6 sUA responder rate is 68.0% in the 16 mg Q4W group and 73.1% in the 30 mg Q4W group.

Safety results from the 2 Q4W cohorts in the FORWARD trial demonstrated the importance of the labeled sUA discontinuation criterion (sUA level > 6 mg/dL at 2 consecutive trial visits) to mitigate the risk of IRs, including anaphylaxis. The Investigator-reported incidence rate of IR or anaphylaxis was 16.0% in the 16 mg Q4W group and 11.5% in the 30 mg Q4W group; however, if the sUA discontinuation criterion had been mandatory per protocol from the beginning of the trial (this criterion was mandated by a protocol amendment) and strictly applied for all participants, the incidence rate of IR/anaphylaxis would have been similar in the 16 mg Q4W group (8.0%) and the 30 mg Q4W group (7.7%).

Consistent with the efficacy data, trough serum concentration (C_{trough}) of pegloticase with 16 mg Q4W and MTX 15 mg was similar to that observed with 8 mg Q2W and MTX 15 mg after multiple doses.

4.5 End-of-Participation Definition

The end-of-participation in this trial is defined as the date of the last participant contact at the 3-month Post-treatment Follow-up.

5 TRIAL POPULATION

5.1 Inclusion Criteria

Eligible participants must meet/provide all of the following criteria:

1. Willing and able to give informed consent
2. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial
3. Adult men or women ≥ 18 years of age
4. Uncontrolled gout, defined as meeting the following criteria:
 - Hyperuricemia during the Screening Period, defined as $sUA \geq 7$ 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 participant interview, and;
 - Symptoms of gout, including at least 1 of the following:
 - Presence of at least 1 tophus
 - Recurrent flares, defined as 2 or more flares in the 12 months prior to Screening
 - Presence of chronic gouty arthritis
5. Willing to discontinue any oral ULT for at least 7 days prior to MTX dosing at Week -4 and continue not receiving any oral ULT when receiving pegloticase/placebo for pegloticase infusions
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; participants 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/placebo for pegloticase or at least 1 ovulatory cycle after the last dose of MTX (whichever is the longer duration after the last dose of pegloticase/placebo for 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 for at least 3 months after the last dose of MTX.

5.2 Exclusion Criteria

Participants 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 Week -4 Visit
3. Severe chronic or recurrent bacterial infections, such as recurrent pneumonia or chronic bronchiectasis
4. Current or chronic treatment with systemic immunosuppressive agents, such as MTX, azathioprine or mycophenolate mofetil; prednisone > 10 mg/day or equivalent dose of other corticosteroid on a chronic basis (3 months or longer)
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. G6PD deficiency (quantitative test at the Screening Visit centrally or locally)
10. Chronic renal impairment, defined as estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m² 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 Week -4
12. Uncontrolled diabetes mellitus
13. 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
14. Prior treatment with pegloticase, another recombinant uricase (rasburicase) or concomitant therapy with a PEG-conjugated drug
15. Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product
16. Contraindication to MTX treatment or MTX treatment considered inappropriate
17. Known intolerance to MTX
18. Unable to tolerate MTX 15 mg orally during the MTX Run-in Period
19. 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
20. Liver transaminase levels (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) > upper limit of normal (ULN) or albumin < the lower limit of normal (LLN) at the Screening Visit
21. Chronic liver disease
22. White blood cell count < 4,000/μL, hematocrit < 32% or platelet count < 75,000/μL
23. HbA1c > 8%
24. Currently receiving systemic or radiologic treatment for ongoing cancer

25. History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of cervix
26. Diagnosis of osteomyelitis
27. Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome
28. 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 participant or interfere with the participant's ability to comply with the protocol requirements or complete the trial
29. Alcohol use in excess of 3 alcoholic beverages per week
30. A known intolerance to all protocol-standard gout flare prophylaxis regimens (i.e., participant must be able to tolerate at least 1 of the following: colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤ 10 mg/day)
31. Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest X-ray may be performed during Screening.

5.3 Lifestyle Considerations

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

5.4 Screen Failures

Participants who do not meet all of the inclusion criteria or meet any of the exclusion criteria between Screening and enrollment (i.e., randomization) on Day 1 will be considered screen failures. Screen failures may be allowed to rescreen or retest laboratory evaluations for the trial if they have not been dispensed trial MTX at Week -4, 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.

Participants who are unable to tolerate the 15 mg dose of MTX during the MTX Run-in Period will be considered MTX Run-in screen failures and will be discontinued from the trial.

5.5 Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Investigational Product

Instructions regarding dose modifications, interruptions and delays are described in Section 6.6.

6 TRIAL INTERVENTIONS AND CONCOMITANT THERAPY

Pegloticase, placebo for pegloticase and MTX are the pre-specified IPs intended to be administered to the trial participants during the trial.

6.1 Trial Interventions Administered

6.1.1 Investigational Products

Trial IPs administered are summarized in Table 1. All participants who satisfy the inclusion/exclusion criteria, complete the MTX Run-in Period and are randomized will receive either pegloticase 16 mg administered IV Q4W from Day 1 through the Week 20 Visit and placebo for pegloticase administered IV Q4W from Week 2 through the Week 22 Visit for a total of 12 infusions or pegloticase 8 mg IV Q2W from Day 1 through the Week 22 Visit for a total of 12 infusions in order to maintain the blind. During the open-label extension, all participants will receive pegloticase 16 mg administered IV Q4W from Week 24 through the Week 44 Visit for a total of 6 infusions. Participants will also receive MTX 15 mg once weekly from Week -4 until prior to the Week 48 Visit.

Table 1 Trial Interventions Administered: IPs

Intervention Name	MTX	Pegloticase	Placebo for Pegloticase
Intervention Description	15 mg orally weekly	IV infusion of a solution Q4W or Q2W	IV infusion of a solution Q4W
Type	Drug	Biologic	Saline
Dose Formulation	2.5 mg tablet	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. Pegloticase will be administered as an admixture of 16 mg (two 8-mg vials) or 8 mg (one 8-mg vial) in 250 mL of 0.45% or 0.9% Sodium Chloride Infusion, USP for IV infusion by gravity feed or infusion pump.	250 mL of 0.45% or 0.9% Sodium Chloride Infusion, USP for IV infusion by gravity feed or infusion pump

Table 1 Trial Interventions Administered: IPs

Intervention Name	MTX	Pegloticase	Placebo for Pegloticase
Unit Dose Strengths	15 mg once weekly from Week -4 until prior to the Week 48 Visit, inclusive	(Double-blind) 16 mg on Day 1 and Q4W thereafter until Week 20, inclusive or 8 mg on Day 1 and Q2W thereafter until Week 22, inclusive (Open-label extension) 16 mg on Week 24 and Q4W thereafter until Week 44, inclusive	(Double-blind) 16 mg arm only: on Week 2 and Q4W thereafter until Week 22, inclusive
Dosage Level(s)	See above	See above	See above
Route of Administration	Oral	IV infusion administered over 120 minutes ($\pm$ 15 minutes)	IV infusion administered over 120 minutes ($\pm$ 15 minutes)
Use	Background intervention	Experimental	Placebo
IP and NIP/AxMP	IP	IP	IP
Sourcing	Provided centrally by Sponsor designee (i.e., PCI Pharma Services)	Provided centrally by Sponsor designee (i.e., PCI Pharma Services)	Provided by the site
Packaging and Labeling	MTX will be packaged in bottles. An ancillary label will be fixed to the bottle that identifies the trial, allows participant information to be entered and contains the investigational use caution statement according to the FDA Title 21 CFR Part 312 requirements. Each bottle and carton (if applicable) label will have a unique number.	Pegloticase (KRYSTEXXA) is commercially available in the US and will be packaged in sterile, single-dose glass vials with a 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 participant 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.	Not applicable

Table 1 Trial Interventions Administered: IPs

Intervention Name	MTX	Pegloticase	Placebo for Pegloticase
Current/Former Names or Aliases	Not applicable	Pegloticase, KRYSTEXXA	Not applicable

AxMP = a medicinal product used for the needs of a clinical trial, but not as an IP (e.g., rescue medication, challenge agent, background treatment); CFR = Code of Federal Regulations; FDA = Food and Drug Administration; IP = investigational product; IV = intravenous; MTX = methotrexate; NIP = non-investigational product; USP = United States Pharmacopeia

6.1.2 Methotrexate

During the MTX Run-in Period (Week -4 Visit to Day 1), all participants will take MTX 15 mg orally weekly. During the MTX Run-in Period, if a MTX 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 participant will be instructed to skip the missed dose and resume at the next regularly scheduled time; thus, participants will be instructed not to double a dose to make up for a missed dose if within 48 hours of the next dose.

At the Day 1 Visit, participants who tolerated MTX will continue taking MTX 15 mg during the double-blind Pegloticase + MTX Period, and through the open-label Pegloticase + MTX Period. Participants will be instructed to take MTX weekly on the same day each week, within 1 to 3 days prior to each pegloticase/placebo for pegloticase infusion; however, if a participant does not do so, MTX must be taken ≥ 60 minutes prior to each pegloticase/placebo for pegloticase infusion. Three additional weekly doses will be taken after the last infusion. If a participant does not tolerate the MTX 15 mg dose after the Day 1 Visit, the dose of MTX may be reduced or discontinued based on pre-specified criteria (Section 6.6.2) and after discussion with the Sponsor Medical Monitor. The participant should remain in the trial.

If the participant discontinues pegloticase due to the sUA discontinuation criterion or other reason, MTX should also be discontinued.

6.1.3 Pegloticase

All participants who meet the eligibility criteria and complete the MTX Run-in Period will receive either pegloticase 16 mg administered IV Q4W from Day 1 through the Week 20 Visit and placebo for pegloticase administered IV Q4W from Week 2 through the Week 22 Visit for a total of 12 infusions or pegloticase 8 mg IV Q2W from Day 1 through the Week 22 Visit for a total of 12 infusions (double-blind Pegloticase + MTX Period). During the open-label extension, all participants will receive pegloticase 16 mg administered IV Q4W from Week 24 through the Week 44 Visit for a total of 6 infusions. Participants will not be fasting on the day of infusion and will be encouraged to have a snack or normal meal before or after the infusion. Pre-infusion sUA results must be reported by the local or central laboratory prior to pegloticase/placebo for pegloticase infusion (see Section 8.2.1). Collection of samples for local determination of sUA levels will begin with the Week 2 Visit. All Day 1 samples for determination of sUA will be sent to the central laboratory.

Standardized IR prophylaxis, consisting of pre-treatment with antihistamines, acetaminophen and corticosteroids, will accompany each infusion (see Section 6.1.5). The drug name, dose and timing of these prophylactic medications will be recorded.

Pegloticase will be administered as an admixture of 16 mg (from two 8-mg vials) or 8 mg (from one 8-mg vial) 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.

In a patent IV site, using tubing with no in-line filter, the pegloticase preparation will be infused over approximately 120 ± 15 minutes while the participant 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 over ~ 15 min to ensure the full dose is administered. The date and time of infusion start and stop and the date and time of IV flush start and stop will be recorded.

Placebo for pegloticase will be 250 mL of 0.45% or 0.9% Sodium Chloride Infusion, USP and will be infused over approximately 120 ± 15 minutes while the participant 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 over ~ 15 min to ensure the full dose is administered. The date and time of infusion start and stop and the date and time of the IV flush start and stop will be recorded. Folic Acid

Participants will take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the Week 48 Visit. Investigators may increase folic acid dose at their discretion.

If the participant discontinues pegloticase due to the sUA discontinuation criterion or other reason, folic acid should also be discontinued.

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

6.1.4 Gout Flare Prophylaxis

It is required that, before a participant begins the double-blind Pegloticase + MTX Period, he or she has been taking at least 1 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 et al, 2020](#)).

Other gout-flare prophylaxis may be allowed if agreed upon by the Sponsor.

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

6.1.5 Infusion Reaction Prophylaxis

Since IRs can occur with pegloticase, all participants will receive IR prophylaxis prior to each infusion, consisting of an antihistamine, acetaminophen and a corticosteroid. To standardize this regimen, participants 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 and 30 minutes, immediately prior to each infusion. Substitution of the corticosteroid is not allowed. For participants receiving placebo for pegloticase, the pre-infusion of methylprednisolone will be replaced with saline before each placebo for pegloticase infusion as there would be no benefit to administration of methylprednisolone and there are risks associated with cumulative glucocorticoid exposure. The methylprednisolone used for IR prophylaxis and the saline which will be used as placebo for methylprednisolone, will be supplied by the site. Other IR medications administered prior to each infusion may also be supplied by the site.

NOTE: If a participant's hemoglobin A1c (HbA1c) is > 6.5% at Screening and/or if a participant has a known diagnosis of diabetes mellitus, the pre-infusion IV steroid dose may be reduced (e.g., methylprednisolone 75 mg IV) after consulting with the Horizon Medical Monitor.

Prescriptions are to be filled at a local pharmacy, as needed. At trial visits, the participant 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 the use of the emergency equipment and in managing IRs will be readily available during, and for 1 hour after, the infusion. As IRs can occur after the completion of the infusion, participants will be observed for 1 hour after the infusion.

6.2 Preparation, Handling, Storage and Accountability

6.2.1 Preparation

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

Pegloticase will be administered as an admixture of 16 mg (two 8-mg vials) or 8 mg (one 8-mg vial) in 250 mL of 0.45% to 0.9% Sodium Chloride Infusion, USP for IV infusion (see IP Manual for details).

Normal saline, single 250 mL bag of 0.45% or 0.9% Sodium Chloride Infusion will be used as placebo for pegloticase. Before administration, the saline will be allowed to reach room temperature.

6.2.2 Storage

Before preparation for use, pegloticase will be stored in the carton, maintained under refrigeration between 2°C and 8°C (36°F and 46°F), 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). Placebo for pegloticase will be stored according to the site's storage procedures.

MTX tablets should be stored at controlled room temperature, per USP, between 20°C and 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F to 86°F).

6.2.3 Accountability

Clinical supplies will be dispensed only in accordance with this protocol. Accurate records of the clinical supplies received, the amount dispensed for each participant and the amount remaining at the conclusion of the trial will be maintained. Each site will also maintain individual participant IP logs/electronic logs to account for MTX tablets dispensed for the MTX Run-in Period and participant compliance will be monitored by the site at each visit (see Section 6.5).

Participants will bring the MTX bottle and MTX dosing calendar to each visit for assessment of compliance. The site will manually count the tablets and re-dispense the bottle to the participant. At the end of the trial or if the participant prematurely discontinues the trial, the participant will return any unused or partially used MTX 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 designated trial team have access.

Please refer to the Trial Pharmacy Manual for more detailed information on MTX and pegloticase/placebo for pegloticase packaging, labeling, storage and destruction.

6.3 Assignment to Trial Intervention

Participants will be randomly assigned in a 1:1 ratio (stratified by presence of tophi based on photographic assessment) to receive either pegloticase 16 mg Q4W with MTX or pegloticase 8 mg Q2W with MTX during the 24-week double-blind period.

Specific procedures for randomization are contained in the trial procedures manual.

6.4 Blinding

This is a 24-week double-blind trial followed by 24-week open-label extension. All participants will receive pegloticase and MTX. To maintain the blind during the double-blind phase, participants in the 16 mg Q4W arm will receive pegloticase 16 mg administered IV Q4W from Day 1 through the Week 20 Visit and placebo for pegloticase IV Q4W from Week 2 through Week 22. For participants receiving placebo for pegloticase, the pre-infusion of methylprednisolone will be replaced with saline before each placebo for pegloticase infusion.

The pharmacist or designee responsible for preparing the pegloticase and placebo solutions for IV administration will not be blinded to the identity of IP. Pharmacist/designee will provide IP in infusion bags (fully diluted for administration) to site personnel with appropriate blinded labels.

The participant, Investigator and all other site personnel will be blinded to the IP being administered on Day 1 and all subsequent trial visits.

The trial blind should be broken only if the safety of a participant is at risk. Unless the participant is at immediate risk, the Investigator must make diligent efforts to contact the Sponsor or Sponsor's designee before unblinding the participant IP assignment. The Investigator must use the interactive response technology (IRT) application to unblind the participant's IP assignment. If the participant's IP is unblinded without prior knowledge of the Sponsor, the Investigator must notify the Sponsor as soon as possible and no later than the next business day. All circumstances surrounding the event must be clearly documented.

The Sponsor or designee will unblind the identity of the IP for an unexpected drug-related SAE for submission to health authorities and Institutional Review Board (IRB) according to the applicable regulatory requirements. However, the results will not be shared with other Sponsor representatives or staff at investigative sites. Details of participants who are unblinded during the trial will be included in the clinical study report. Unblinding for independent pharmacological analysis of biological samples or SAE reporting will be performed according to procedures in place to ensure integrity of the data.

With the exception of the unblinded pharmacist/designee, all investigative site staff directly involved in this trial will remain blinded from randomization through analysis of the final data and all site close-out visits. The Sponsor and select designees will remain blinded until after the database lock for the primary analysis following completion of all participants in the double-blind Pegloticase + MTX Period.

6.5 Trial Intervention Compliance

A dosing calendar will be provided to participants at the Week -4 Visit for recording the doses 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 visit for assessment of compliance. Adherence to the MTX regimen will also be recorded in the eCRF by the trial coordinator at trial visits by recording the date of each MTX dose (mg), frequency and time of each dose per calendar day. Participants who have taken at least 80% of the protocol-specified amount of MTX will be considered compliant. Noncompliant participants will be re-educated on compliance.

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

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

6.6 Dose Modification

The doses of pegloticase and MTX to be administered are described in Section [6.1](#).

6.6.1 Pegloticase Modifications

Infusion of pegloticase/placebo for pegloticase will be immediately held if the participant 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 following an IR in an individual participant may be given in a larger volume of diluent, not to exceed 500 mL. In this case, the infusion duration will also be extended to a minimum of 3 hours. The total volume and duration of infusion will be captured in the medical record and eCRF.

Infusion of pegloticase/placebo for pegloticase may be held or delayed if the participant has an ongoing SAE or AE/SAE that occurs just prior to the infusion. In this situation, the Investigator will discuss the status of the participant with the Sponsor's Medical Monitor on a case-by-case basis to determine whether the participant should continue to the next scheduled infusion or proceed to the End of Pegloticase Infusions Visit.

6.6.2 MTX Dose Titration Algorithm and Intolerance Criteria

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

1. Abnormal hematology findings:
 - a. $WBC < 3.5 \times 10^9/L$
 - b. $Platelets < 75 \times 10^9/L$
 - c. $Hematocrit < 32\%$
2. Abnormal hepatic function findings:
 - a. $AST/ALT > 1.5 \times$ upper limit of reference range and
 - b. $Albumin < LLN$
3. Abnormal renal function: $eGFR < 30 \text{ mL/min/1.73 m}^2$ (as estimated with the Modified Diet in Renal Disease [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 or mild gastrointestinal discomfort, the Investigator may increase the folic acid dose (e.g., to 2 mg daily) or recommend a divided dose of MTX (e.g., 3 tablets of 2.5 mg in the morning and evening on the day of dosing); if symptoms improve, the participant will not be considered a screen failure on the basis of that symptom.

During the double-blind and open-label extension Pegloticase + MTX Periods, MTX dose guidance based on new laboratory findings or new symptoms is summarized in Table 2.

Table 2 MTX Dose Guidance Based on New Laboratory Findings or New Symptoms During the Double-blind and Open-label Extension Pegloticase + MTX Periods

Laboratory Parameter	Value	MTX Dose Change
White blood cell count	$3.0 \times 10^9/\text{L} \sim 3.5 \times 10^9/\text{L}$	Decrease to 10 mg
	$< 3.0 \times 10^9/\text{L}$	Temporary stop
Platelets	$< 50 \times 10^9/\text{L}$	Temporary stop
Hematocrit	$< 27\%$	Temporary stop
Alanine aminotransferase/aspartate aminotransferase	1.5 to $2 \times \text{ULN}$	Decrease to 10 mg
	$> 2 \times \text{ULN}$	Temporary stop
Estimated glomerular filtration rate	$< 30 \text{ mL/min/1.73 m}^2$	Temporary stop
New clinically important symptoms/signs ^a	Yes	Temporary stop

MTX = methotrexate; ULN = upper limit of normal

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

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

1. ALT/AST $> 1.5 \times \text{ULN}$ on 3 of any 5 consecutive measures
2. Albumin $< 0.8 \times \text{LLN}$ 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 Investigator

Guidance for increasing MTX back to 15 mg after dose reduction, based on improvement or resolution of abnormal liver enzymes ($> 2 \times \text{ULN}$), is as follows:

1. When liver enzymes return to values $\leq 1.5 \times \text{ULN}$, increase the MTX dose by 2.5 mg and reassess in 2 weeks.
2. If liver enzymes remain $\leq 1.5 \times \text{ULN}$, increase the 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 to 15 mg weekly, based on Investigator judgement and in discussion with the Sponsor Medical Monitor.

6.6.3 Gout Flare Treatment

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including pegloticase. Participants 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 (see Section 8.3.5). All participants who experience a gout flare during the trial will be prescribed anti-inflammatory treatment (e.g., non-steroidal anti-inflammatory drug, colchicine, corticosteroids and intra-articular steroid injections), as clinically indicated or deemed necessary on an individual basis at the discretion of the Investigator. Pain medications for gout flare should be administered according to standard of care as clinically indicated or deemed necessary on an individual basis at the discretion of the Investigator. All medications should be documented on the concomitant medication eCRF.

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

6.6.4 Infusion Reaction Treatment

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

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

- A physical examination will be performed to capture medically relevant details, including, but not limited to, a thorough dermatologic examination for detection of erythema, urticaria (hives) or peri-oral or lingual edema; a chest examination for breath sounds, stridor or wheezing; and a cardiac examination with attention to irregular heartbeat.
- Vital signs (sitting or supine blood pressure, heart rate, respiratory rate and body temperature) will be captured at least every 30 minutes until the resolution or stabilization of the AE.
- A serum sample will be collected in a serum-separating tube at that time or at the subsequent visit. The sample will be centrifuged, frozen at -20°C or colder and stored for the batch shipment to a Horizon-designated laboratory for evaluation of pegloticase antibodies at a future date.
- When possible, a 12-lead electrocardiogram (ECG) will also be performed at the time of IR.

If, in the Investigator's opinion, the participant is experiencing an anaphylactic reaction (see Section 8.4.8), 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/placebo for 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 8.4.8) 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.

6.7 Continued Access to IP after the End of the Trial

There will be no continued access to IP after the end of the trial.

6.8 Treatment of Overdose

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

All cases of medication errors and overdose (with or without associated AEs) will be documented on the eCRF 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 10.2.3 and Section 8.4.4, respectively.

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

6.9 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 IPs (or prior gout medications) taken by a participant from Screening through the Post-treatment Follow-up Visits. These include 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.

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

6.9.1 Restricted Therapy and Medications

Restrictions pertaining to prior/current therapy per the exclusion criteria are detailed in Section 5.

Participants should not receive the following medications for at least 7 days prior to MTX dosing at Week -4 and while receiving pegloticase/placebo for pegloticase infusions:

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

Participants 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 MTX other than the trial IP, 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

Treatment with antibiotics might increase MTX toxicity or pre-dispose to new or worsening infection; therefore, MTX should be temporarily stopped during antibiotic use.

7 DISCONTINUATION OF IP AND PARTICIPANT WITHDRAWAL

All participants 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 participant from IP or from the trial at any time if further participation in the trial is not in the best interest of the participant. However, participants who are removed from pegloticase therapy should remain on trial barring withdrawal of consent for trial participation.

7.1 Discontinuation of Pegloticase

In addition to completion of pegloticase through Week 44, the reason for discontinuation of pegloticase should be recorded on the eCRF using 1 of the following categories:

- Lost to follow-up. The participant does not return to the clinic for scheduled assessments and does not respond to the site's attempts to contact the participant.
- Lack of efficacy (i.e., sUA > 6 mg/dL at 2 consecutive trial visits beginning with the Week 2 Visit)
- AE. The participant experiences an AE that imposes an unacceptable risk to the participant's health (e.g., anaphylactic reaction, or the participant is unwilling to continue pegloticase because of an AE). Participants 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 participant (specify reason).
- Withdrawal by participant. Participant refusal of additional therapy (specify reason).
- Trial terminated by Sponsor. The Sponsor, IRB or regulatory agency terminates the trial.
- Pregnancy
- Death

Trial considerations for participants ending infusions of IP prior to Week 44 are as follows:

- MTX, along with folic acid, will be discontinued at the time of cessation of IP infusions prior to Week 44.
- All participants will complete the End of Pegloticase Infusions Visit and will remain in the trial through Week 48 regardless of whether they stop infusions due to the sUA discontinuation criterion or other reason (e.g., withdrawal of consent for pegloticase infusions).
- Participants should continue to participate in all visits through the end of the trial. Participants are especially encouraged to complete trial visits at the trial site during key efficacy and safety collections at Weeks 8, 10, 12, 20, 21, 22, 23, 24, and 48/EOT/Early Termination (ET), so that sample collection for sUA and other key assessments can be completed. During visits between these key efficacy and safety collection visits, participants who have stopped infusions may complete trial visits in person or via telephone to collect AE, concomitant medication and gout flare information.

- Activities related to pre-/post-infusion monitoring or medication dispensation will not be completed once a participant has stopped pegloticase infusions. These activities include:
 - MTX compliance/reconciliation
 - IR prophylaxis
 - IR prophylaxis compliance
 - Folic acid compliance
 - Pegloticase/placebo for pegloticase infusion
 - Pegloticase PK sampling
 - Pre-infusion MTX polyglutamate sampling
 - MTX drug/dispensation related items
- Re-introduction of oral ULT should not start until after the End of Pegloticase Infusions Visit laboratory tests are collected.

7.2 Participant Early Withdrawal from the Trial

Participants are free at any time to withdraw from the trial (IP and assessments) without prejudice to further treatment (withdrawal of consent). Such participants will always be asked about the reason(s) for withdrawal and the presence of any AEs. AEs will be followed up. Participants who withdraw should undergo an ET visit, as shown in Section 1.3, if consent for this visit is not also withdrawn. If a participant withdraws consent to participate in the trial, then no further trial visits or data collection should take place.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the trial, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site trial records.

In addition to completion of therapy and designated trial visits through Week 48, the reason for discontinuation from the trial should be recorded on the eCRF using 1 of the following categories:

- Lost to follow-up. The participant does not return to the clinic for scheduled assessments and does not respond to the site's attempts to contact the participant.
- Withdrawal of consent. The participant withdraws from the trial. The site should attempt to determine the underlying reason for the withdrawal and specify the reason on the eCRF (e.g., AE, voluntary withdrawal).
- Trial terminated by Sponsor. The Sponsor, IRB or regulatory agency terminates the trial.
- Death

No participant in the trial can receive commercially available KRYSTEXXA. Any participant who discontinues pegloticase should be followed to the end of the trial and CANNOT receive commercial KRYSTEXXA. A participant would be required to withdraw from the trial if the plan is to ignore this dosing rule and receive commercial KRYSTEXXA.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (if possible, 3 telephone calls and, if necessary, a registered letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the trial.
- Site personnel or an independent third party will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

7.4 Replacement

7.4.1 Participants

In general, participants who prematurely discontinue from the trial for any reason will not be replaced.

7.4.2 Centers

A center may be closed and/or replaced for excessively slow recruitment, poor protocol adherence, or other reason as necessary according to the Sponsor

8 TRIAL ASSESSMENTS AND PROCEDURES

8.1 Administrative and General/Baseline Procedures

Screening and Baseline assessments are listed in Section 1.3. All assessments will be completed prior to the pegloticase/placebo for pegloticase infusions, with the exception of the following assessments which are also required to be conducted post-infusion: post-infusion sUA, post-infusion PK, and post-infusion vital signs (please refer to Section 1.3 footnotes for specific details).

Demographic data, medical/surgical/substance use history and medication use history will be collected at Screening, and a chest X-ray (if not available within 2 years prior to Screening and deemed necessary by the Investigator) and a G6PD test will be performed. Eligibility criteria will be evaluated at Screening, Week -4, Week -2 and Day 1.

8.2 Efficacy and Quality-of-Life Assessments

The planned timing of efficacy (sUA, digital photography (hands and feet), physician global assessment) and quality-of-life (HAQ) assessments is provided in Section 1.3.

8.2.1 Serum Uric Acid

Serum samples for measurement of sUA levels will be collected and sent to the central laboratory at the Screening Visit, the Week -4 Visit (prior to the first dose of MTX) and the Week -2 Visit during the MTX Run-in Period. On all infusion visit dates starting at Day 1, a pre-infusion and post-infusion sUA will be collected to be shipped to the Central Laboratory. Additional serum samples for sUA levels will be collected at non-infusion visits at Weeks 21, 23, 26, 30, 34, 38, 42, 46, the End of Pegloticase Infusions Visit (if applicable), the Week 48/EOT/ET Visit and 3-month Follow-up Visit and sent to the Central Laboratory. For all infusion visits beginning at Week 2 during the double-blind and open-label extension Pegloticase + MTX Periods, 1 sUA sample will be collected locally within 48 hours PRIOR to each infusion visit until the Week 44 Visit for determination by a local laboratory if the sUA discontinuation criterion has been met. See the Laboratory Manual for instructions.

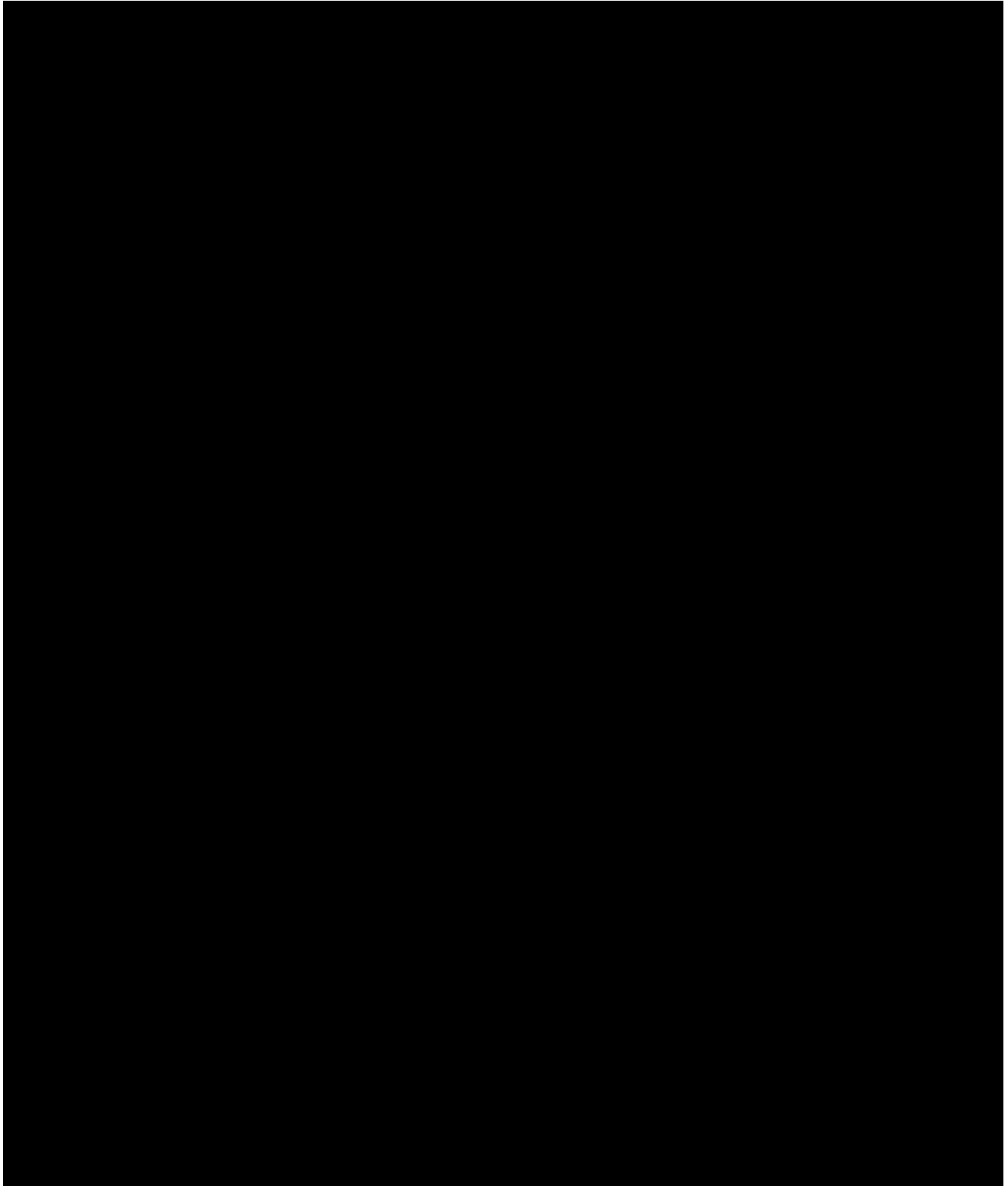
Additional serum samples for sUA levels will be collected at non-infusion visits at Weeks 21, 23, 26, 30, 34, 38, 42, 46, the End of Pegloticase Infusions Visit (if applicable), the Week 48/EOT/ET Visit, and 3-month Follow-up Visit, as indicated in Section 1.3.

Participants with a pre-infusion sUA level > 6 mg/dL at 2 consecutive trial visits beginning with the Week 2 Visit will discontinue pegloticase but remain in the trial to complete the scheduled assessments.

If a local sUA result cannot be obtained within 48 hours of the infusion (beginning at Week 2), the Medical Monitor will be consulted to obtain approval prior to proceeding with the planned infusion. The pre-infusion sUA (local) sample for the local laboratory will be collected, if possible, prior to the infusion.

If a participant's previous visit sUA (local or central laboratory) is < 6 mg/dL, it will be allowable to collect the local pre-infusion sUA sample on the same day and similar time as the sample to be sent to the central laboratory. However, if the prior visit sUA sample is > 6 mg/dL

(local or central laboratory), a local sUA sample will be collected with the result available prior to the pegloticase/placebo for pegloticase infusion to be certain the participant does not meet the sUA discontinuation criterion.



8.3 Safety Assessments

The planned timing of safety assessments is provided in Section 1.3.

8.3.1 Vital Signs, Height and Weight

Routine vital signs include blood pressure, respiratory rate, temperature and heart rate. Heart rate and blood pressure measurements should be taken after the participant has been in a sitting position and in a rested and calm state for at least 5 minutes with proper positioning, including back support and feet flat on the floor. The participant's arm should be supported at heart level and the cuff placed on a bare arm. A large cuff should be used, as needed, to fit the upper arm and the same arm is to be used at each trial visit. The Korotkoff phase V will be used to determine diastolic blood pressure. During the double-blind and open-label extension Pegloticase + MTX Period visits, vital signs should be taken before the pegloticase/placebo for pegloticase infusion and any time after the end of the infusion, but prior to participant's discharge/release from the site.

When possible, the same staff member should take all BP measurements for a given participant.

Weight should be measured in kilograms or pounds while the participant is not wearing shoes. Weight should be measured pre-infusion at all visits that vital signs are collected.

Height will be recorded at the Screening Visit only.

Vital sign monitoring during IR is described in Section 6.6.4.

8.3.2 Physical Examinations

A complete physical examination will be performed at the Screening Visit, including assessment of head, ears, eyes, nose, throat, heart, lungs, abdomen, skin, extremities, neurological status, and the musculoskeletal system.

A targeted physical examination per Investigator judgement will be conducted at the time points indicated in Section 1.3; at a minimum, this should include examination of the heart, lungs and abdomen.

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

8.3.3 Electrocardiogram

A 12-lead ECG will be performed at Screening and at the discretion of the Investigator thereafter. When possible, a 12-lead ECG will also be performed when an AESI (Section 8.4.8) of IR, anaphylaxis or cardiovascular event is suspected.

8.3.4 Clinical Safety Laboratory Tests

Clinical safety laboratory test will include:

- Hematology: complete blood count with differential (hemoglobin concentration, hematocrit, erythrocyte count, platelet count, leukocyte count and differential leukocyte count)
- Chemistry: albumin, transaminases (AST, ALT), alkaline phosphatase, total bilirubin, creatinine including calculation for eGFR calculated by the MDRD study equation:
 $175 \times (\text{Scr}_{[\text{mg/dL}]})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$ or
 $175 \times (\text{Scr}_{[\mu\text{mol/L}]/88.4})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$, glucose, sodium, potassium, calcium, chloride, total protein, blood urea nitrogen and human chorionic gonadotropin (at the Screening Visit for all female participants of childbearing potential), hs-CRP, HbA1c

Guidance on Blood Glucose Monitoring: HbA1c testing must be performed at Screening for all participants. Participants that are diabetic and/or with elevated HbA1c's at Screening will be assessed and monitored for elevated blood glucose and symptoms of hyperglycemia prior to methylprednisolone infusion and after pegloticase infusion.

Glucose levels will be measured via finger prick test. If HbA1c > 6.5% and/or if subject has known diagnosis of diabetes mellitus, additional measures are recommended:

- HbA1c every 3 months during the trial, see Section 1.3 for specific visits
- Investigator asked to closely monitor glucose levels and adjust any diabetic medications as necessary
- Participant should consult their primary care physician and/or Endocrinologist managing their diabetes

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

Participants with clinically significant hyperglycemia (as determined by Investigators and/or the Sponsor) or pre-existing diabetes must be under appropriate glycemic control

before and while receiving pegloticase. Additional information including relevant medical history and HbA1c level must be collected for subjects with clinically significant hyperglycemia.

- Urine: albumin:creatinine ratio and human chorionic gonadotropin for all female participants 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.

8.3.5 Gout Flare

There is no validated instrument to assess gout flares. Gout flares will be assessed at the time points specified in Section 1.3. Investigators will assess gout flares based on participant self-reporting, with Investigator confirmation of flare based on participant questioning and/or direct observation. All gout flares will be recorded as AEs with the required AE reporting information. Investigators will also ask the participant a series of questions related to each gout flare to document participant report of swollen joints, joints that are warm to touch and level of joint pain (Gaffo et al, 2012).

8.3.6 Pregnancy Testing

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]) 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 1.3.

Participants who receive at least 1 dose of MTX and are females of childbearing potential will receive a safety follow-up phone call/email approximately 30 days after the last dose of MTX to verify at least 1 ovulatory cycle has occurred after the last dose of MTX. If the participant has not ovulated, a urine pregnancy test will be performed. For those participants who receive at least 1 dose of MTX and are non-vasectomized males, a phone/email inquiry will be conducted 3 months after MTX discontinuation regarding partner pregnancy (inquiry can occur during the 3-month Post-treatment Follow-up).

8.3.7 Adjudication Committee

One independent external clinical adjudication committee will be established for this trial to adjudicate the AESIs of IR, anaphylaxis and MACE. The AESI of gout flare will not be adjudicated. The committee will be comprised of physicians with experience in immunology, allergic reactions, rheumatology and cardiovascular diseases. Details outlining the responsibilities of the adjudication committee will be included in the adjudication committee charter.

8.4 Adverse Events, Serious Adverse Events and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.2.1 and Section 10.2.2, respectively.

The method of recording, evaluating and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.3 and Section 8.4.4, respectively.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

AE and SAE monitoring will begin from signing of the informed consent form (ICF) until the 3-month Post-treatment Follow-up Visit.

All participants will receive a safety follow-up phone call/email approximately 30 days after the last dose of pegloticase/placebo for pegloticase to assess if any SAEs have occurred.

All SAEs will be recorded and reported to the Sponsor immediately, as detailed in Section 8.4.4.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the trial. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and the Investigator considers the event to be reasonably related to the IP or trial participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial recording of an AE, the Investigator should proactively follow the participant. Any non-serious AE that is ongoing at the 3-month Post-treatment Follow-up Visit should be reviewed to determine if further follow-up is required. The Investigator will document on the AE eCRF all ongoing non-serious AEs that will not be followed further after the 3-month Post-treatment Follow-up Visit. If in doubt, the Investigator should consult the Sponsor's Medical Monitor.

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

8.4.4 Regulatory Reporting Requirements for SAEs

All SAEs beginning with the time of signing of the ICF and continuing until 30 days after trial discharge must be reported. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to an IP:

1. Report the SAE to the Sponsor by submitting a completed SAE report form by email or fax **immediately, without undue delay, but no later than 24 hours** after becoming aware that a participant has experienced an SAE (see Section 10.1.1 for contact information).

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 the 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 IP. The Sponsor will determine whether the SAE is unexpected in nature.
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.

8.4.5 Pregnancy

Information must be obtained and reported if a female participant suspects that she has become pregnant during the trial (including the MTX Run-in Period) up to 30 days after the last dose of IP (either pegloticase/placebo for pegloticase or MTX), or if a female partner of a male participant suspects that she has become pregnant during the trial (including the MTX Run-in Period) up to 3 months (approximately 90 days) after her male participant partner discontinues MTX. The Investigator will instruct the female participant to stop taking all IPs. A serum pregnancy test should be performed if any female participant or female partner of a male participant suspects that she has become pregnant during the time frame, as defined above. If pregnancy is confirmed, the female participant will be removed from pegloticase therapy and should remain in the trial barring withdrawal of consent for trial participation. Pregnancy will be followed up until the outcome of pregnancy is known.

Complete pregnancy information, including the outcome of the pregnancy, should be collected in the source documents and pregnancy outcome form for the female participant or partner of a male participant. In the absence of complications, follow-up after delivery will be no longer than 8 weeks. Any stillbirth or premature termination of pregnancy, whether elective, therapeutic or spontaneous, should be reported on the pregnancy outcome form. Any pregnancy complication, 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 defect in the newborn. Any SAE occurring as a result of a post-trial pregnancy and considered reasonably related to IP by the Investigator should be reported to the Sponsor.

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

8.4.6 Cardiovascular and Death Events

Major cardiovascular events are considered AESIs (see Section 8.4.8). Deaths are considered SAEs (see Section 10.2.2).

8.4.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

A disease-related event or outcome that meets the definition of AE or SAE will be recorded as such.

8.4.8 Adverse Events of Special Interest

AEs of special interest include IRs, anaphylaxis, gout flares and cardiovascular events. An independent external adjudication committee will review reported events of IR, anaphylaxis and MACE.

Infusion Reaction

An IR will be defined as any infusion-related AE or cluster of temporally related AEs, not attributable to another cause, that occur during the pegloticase/placebo for 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 Investigator's discretion. Signs and symptoms of the IR and treatments administered will be documented in the medical record and in the eCRF.

Examples of AEs not considered possible IRs include, but are not limited to, laboratory abnormalities that are unlikely to have occurred during or within 1 hour following the infusion (e.g., anemia), gout flares, most infectious diseases or the recurrence or worsening of a known chronic medical problem identified in the participant'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 participant (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 participant (minutes to several hours): systolic blood pressure < 90 mmHg or $> 30\%$ decrease from that participant's baseline

Gout Flares

It is common for potent ULTs to lead to acute attacks of gout. Gout flares will be confirmed through questioning or direct observation, as detailed in Section [8.3.5](#).

Major Cardiovascular Events

Cardiovascular AEs (MACE) will be collected as part of the AE collection. The adjudication committee will adjudicate all MACE, which include type I and type II non-fatal myocardial infarction, non-fatal stroke, cardiovascular death and congestive heart failure.

8.5 Pharmacokinetics

Serum samples for PK analysis of pegloticase will be collected after the end of infusion on Day 1 (prior to discharge); prior to the pegloticase/placebo for pegloticase infusion and after the end of infusion (prior to discharge) at Weeks 2, 4, 8, 12, 20, 22, 24 and 36. Additional PK samples will be collected at the following non-infusion visits: End of Pegloticase Infusions Visit (if applicable) and Week 48/EOT/ET Visit.

Blood samples will be collected for MTX polyglutamate analysis prior to the pegloticase infusion on Day 1, Week 12, Week 24 and Week 36.

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.

8.6 Pharmacodynamics

No evaluation of pharmacodynamics is planned.

8.7 Mechanistic/Disease and Exploratory Biomarkers Evaluation

Serum, plasma, and urine will be assessed for biomarkers related to the mechanism of action of pegloticase and factors associated with gout activity. Intended purpose and biomarker analysis include but are not limited to the proteomic evaluation of gout-flare inflammatory mediators and cardiometabolic markers to inform trial findings (as needed). Serum, plasma and urine will be collected during Screening and prior to pegloticase/placebo for pegloticase infusion at Day 1, Weeks 2, 4, 8, 12 and 24, and at any time during the Week 48/ET/EOT and 3M FU visits. Remaining exploratory biomarker samples may be used for future research. For subjects where no Day 1 pre-infusion samples were collected, biomarker samples will not be collected at the subsequent visits.

Each sample collection date and time will be recorded in source documents. Detailed instructions regarding blood sample timing and handling are provided in the Laboratory Manual.

8.8 Genetics

Genetics (DNA) will not be evaluated in this trial.

8.9 Immunogenicity Assessments

Serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies will be collected prior to the pegloticase infusion on Day 1, Weeks 4, 8, 12, 20, 24 and 36. Additional samples will be collected at the following non-infusion visits: End of Pegloticase Infusions Visit (if applicable) and Week 48/EOT/ET Visit. In the event of an AE suspected to be an IR, a serum sample will be collected at that time or at the subsequent visit for evaluation of pegloticase antibodies.

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.

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters will not be evaluated in this trial.

9 STATISTICAL CONSIDERATIONS

This section is a summary of the planned statistical analyses. A comprehensive statistical analysis plan (SAP) will be prepared and any subsequent amendments will be documented, with final amendments completed prior to database lock for the primary analysis (refer to Section 9.4 for details). Any deviations from this plan will be reported in the clinical study report.

9.1 Statistical Hypotheses

The primary objective is to demonstrate that pegloticase 16 mg Q4W with MTX is non-inferior to pegloticase 8 mg Q2W with MTX in achieving sustained normalization of sUA < 6 mg/dL for at least 80% of the time during Month 6.

Hypotheses to be tested in relation to the primary estimand are as follows:

$$H_0: \pi_c - \pi_t \geq 0.2 \text{ vs } H_A: \pi_c - \pi_t < 0.2,$$

where π_t = proportion of responders during Month 6 for pegloticase 16 mg Q4W with MTX
 π_c = proportion of responders during Month 6 for pegloticase 8 mg Q2W with MTX

- Null hypothesis: pegloticase 16 mg Q4W with MTX is inferior to pegloticase 8 mg Q2W with MTX in achieving the sustained normalization of sUA < 6 mg/dL for at least 80% of the time during Month 6 by 20% or more.
- Alternative hypothesis: pegloticase 16 mg Q4W with MTX is not inferior to pegloticase 8 mg Q2W with MTX in achieving the sustained normalization of sUA < 6 mg/dL for at least 80% of the time during Month 6 by 20% or more.

9.1.1 Multiplicity Adjustment

To control the overall Type I error rate of the trial, the secondary efficacy endpoint will be tested sequentially only if non-inferiority is achieved for the primary efficacy endpoint.

9.2 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full Analysis Set (FAS)	All participants who receive at least 1 dose of pegloticase
MTX Analysis Set (MAS)	All participants who receive at least 1 dose of MTX
Safety Analysis Set (SAS)	All participants who receive at least 1 dose of pegloticase
PK Analysis Set	All participants who receive at least 1 dose of pegloticase and have at least 1 quantifiable serum PK observation post-first dose

The FAS will be used to analyze endpoints related to the efficacy objectives. The MAS and SAS will be used to analyze the endpoints and assessments related to safety in each treatment period.

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety and PK analyses, participants will be included in the analyses according to the investigational intervention they actually received.

9.3 Statistical Analyses

9.3.1 General Considerations

In general, tabular summaries will be presented by the treatment group (pegloticase 16 mg Q4W + MTX and pegloticase 8 mg Q2W + MTX) and treatment period. For continuous data, number of participants, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum will be reported. For categorical data, percentage and frequency will be reported. Data listings will be sorted by treatment group and participant number.

Baseline is defined as the last observation prior to the first dose of pegloticase, unless otherwise specified.

9.3.2 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the proportion of responders during Month 6. A responder is defined as a participant for whom the proportion of time that the sUA-time curve is < 6 mg/dL during the analysis interval is at least 80%.

The primary estimand for the primary endpoint is defined by the following:

Population	FAS
Intercurrent event (ICE)	Early discontinuation of pegloticase; meeting sUA discontinuation criterion (sUA values > 6 mg/dL at 2 consecutive scheduled visits [excluding post-infusion sUA] starting at Week 2)
ICE strategy	Participants who meet the sUA discontinuation criterion, have only 1 sUA observation or have no sUA during Month 6 are considered treatment failures (non-responders). Available sUA results during Month 6 from participants who discontinue pegloticase for reasons other than meeting the sUA discontinuation criterion prior to Week 24 will be used in the response calculation.
Population-level summary	Difference in response rate between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX

The primary efficacy analysis will be conducted on the FAS. The proportion of time that the sUA level is below 6 mg/dL is defined as the ratio of the time during which the sUA level remains below 6 mg/dL (using linear interpolation, if necessary) during the entire Month 6 interval. A participant will be declared a non-responder if the participant had an sUA level > 6 mg/dL at 2 consecutive trial visits prior to or during Month 6 beginning with the Week 2 Visit.

The primary endpoint will be analyzed using g-computation to estimate the covariate adjusted unconditional treatment effect with 95% CI (Ye et al., 2023). Logistic regression will be used as the working model in the g-computation procedure with treatment and covariates (including but not limited to) for tophi presence (present, not present), age, and baseline eGFR. Details of the covariates and analysis methods will be pre-specified in the SAP. The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups ($\pi_c - \pi_t$) is less than the non-inferiority margin of 20%.

Previous registrational trials indicated a responder rate of approximately 44% in the pegloticase monotherapy group, while the placebo group had no responders. In MIRROR-RCT ([NCT0399473](#)), the pegloticase 8 mg Q2W + MTX co-administration group exhibited a responder rate of 74% (95% CI: 64%, 82%) compared to a 41% responder rate in the pegloticase 8 mg Q2W monotherapy group (between-group difference [95% CI]: 33% [17%, 49%]) in participants who received pegloticase. This trial will enroll participants from the same gout population as MIRROR-RCT and has a nearly identical study design as well as inclusion and exclusion criteria. The primary endpoint (the proportion of responders during Month 6) is the same as the MIRROR-RCT primary endpoint, and missing data and intercurrent events will be handled in the same manner. Therefore, it is reasonable to anticipate that the active-controlled group will have a responder rate similar to that of MIRROR-RCT.

There are no prior trials comparing pegloticase co-administered with MTX vs. placebo. However, patients with uncontrolled gout would not be expected to maintain sUA < 6 mg/dL without treatment and so a 0% response rate in untreated patients, as seen in the registrational trials, is reasonable. Considering an effect size of 65% compared with placebo, a non-inferiority margin of 20% was chosen to preserve 69% of the effect vs. placebo, and also a similar amount of the effect observed in the active-controlled group compared with the pegloticase monotherapy group.

9.3.3 Secondary Endpoint Analysis

The key secondary efficacy endpoint is the proportion of participants with complete resolution of ≥ 1 tophus (using digital photography) at Week 24 in participants with tophi at Baseline. The primary estimand for this endpoint is defined by the following:

Population	FAS with tophus (or tophi) present at Baseline
ICE	Early discontinuation of pegloticase
ICE strategy	Tophi data collected after a participant has discontinued from pegloticase will be included in analysis.
Population-level summary	Difference in the proportion of participants with complete resolution of ≥ 1 tophus at Week 24 between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX

The proportion of participants with resolution of ≥ 1 tophus (100% decrease in the area of at least 1 tophus) at Week 24 will be analyzed using the same g-computation procedure used for the primary endpoint to estimate the covariate adjusted unconditional treatment effect with 95% CI. Logistic regression will be used as the working model in the g-computation procedure with treatment and covariates (including but not limited to) for age, and baseline eGFR. The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups is less than the non-inferiority margin of 15%.

In MIRROR-RCT ([NCT0399473](#)), the pegloticase 8 mg Q2W + MTX co-administration group exhibited a tophus resolution rate of 35% at Week 24 compared to 13% in the pegloticase 8 mg Q2W monotherapy group (between-group difference [95% CI]: 21% [3%, 39%]) in participants

with tophi at baseline (N=52 and 29, respectively). While there are no prior placebo-controlled trials with the active control, untreated patients would not be expected to have tophus resolution. Considering an effect size of 30% compared with placebo, a non-inferiority margin of 15% was chosen to preserve 50% of the effect vs. placebo.

9.3.4 Pharmacokinetic Analyses

Concentrations of pegloticase will be summarized using descriptive statistics for the PK Analysis Set. Further, the mean and percent coefficient of variation (CV%) of pegloticase concentrations will be provided by visit and treatment group in the subset of participants who are ADA positive (defined as positive for anti-PEG or anti-uricase antibodies at any visit during the trial) and ADA negative (defined as negative for both anti-PEG and anti-uricase antibodies for all visits during the trial).

Concentrations of MTX polyglutamate will be measured for 5 active metabolites (MTX-PG1, MTX-PG2, MTX-PG3, MTX-PG4, MTX-PG5) and summarized.

9.3.5 Immunogenicity Analyses

Using the SAS, the number and percentage of participants ADA positive and ADA negative at Baseline for anti-PEG and anti-uricase IgG antibodies will be summarized. The number and percentage of participants who develop positive ADA as well as the titer of positive ADA will be summarized by treatment group and by visit.

9.3.6 Safety and Tolerability Analyses

The incidences of treatment-emergent AEs (TEAEs), including SAEs, TEAEs leading to discontinuation of IP (MTX or pegloticase) and TEAEs of special interest, will be summarized by treatment period.

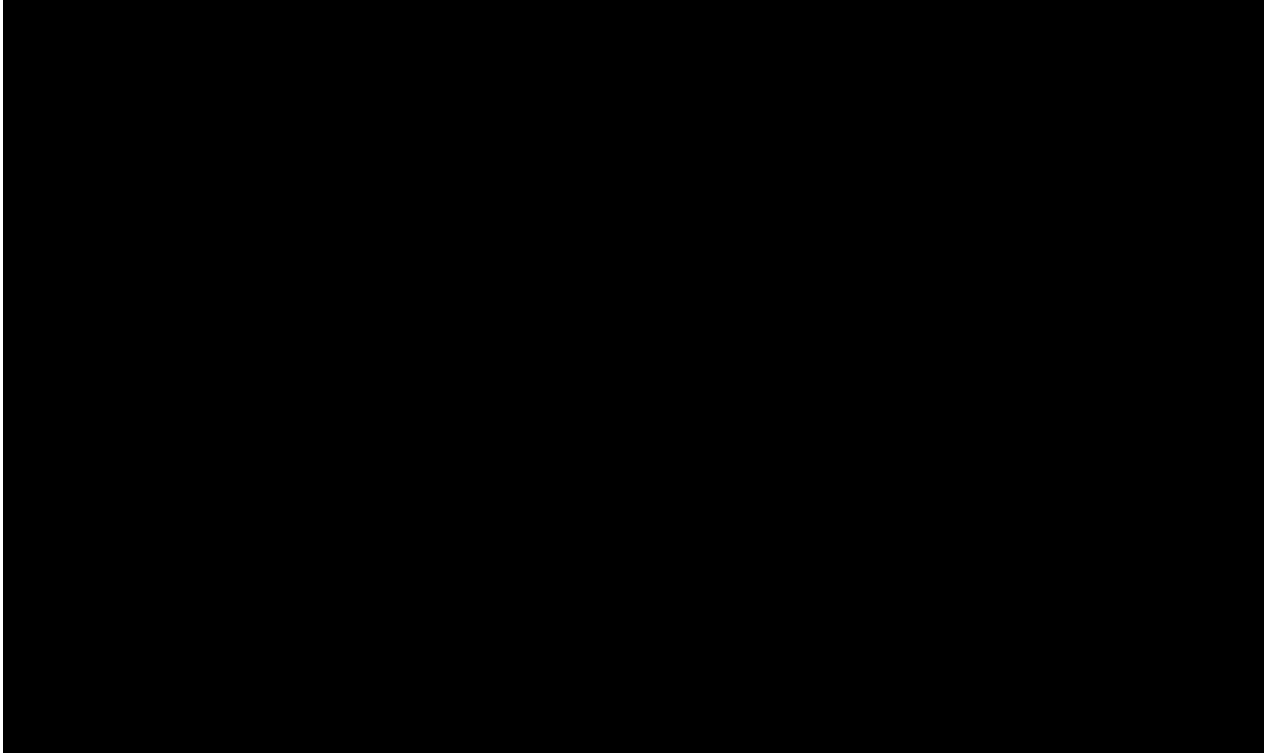
AEs during the double-blind and open-label extension Pegloticase + MTX Periods will be summarized by treatment group (pegloticase 16 mg Q4W with MTX and pegloticase 8 mg Q2W with MTX). AEs during the open-label extension period will be summarized by treatment received during the double-blind period and overall. AEs with an onset date more than 30 days after the last dose of pegloticase/placebo for pegloticase and/or MTX (whichever is later) will be AEs in the Follow-up Period.

Summaries by severity and relationship to MTX and pegloticase will also be provided. Summaries of TEAEs by system organ class and preferred term will be provided. In addition, the number and percentage of participants with adjudicated IRs, including anaphylaxis, will be summarized overall and by severity of event using various categories of ADA status. The number and percentage of participants experiencing gout flares will be summarized by month of occurrence and by 3-month periods.

Laboratory test results will be summarized by trial visit and change from Baseline and also classified relative to the normal reference range (normal, low or high). Shift tables for select laboratory parameters by reference range (normal, low or high) and by Common Terminology Criteria for Adverse Events grade (if available) will be provided. Vital signs will be summarized by visit, change and % change from Baseline. Analyses will include laboratory test results and

vital sign data collected within 30 days of the last dose of MTX and/or pegloticase/placebo for pegloticase, whichever is later.

9.3.7 Exploratory Analyses



9.4 Interim Analysis

The primary analysis of efficacy is planned after all participants complete the Week 24 Visit, the timepoint for the primary efficacy endpoint, in the double-blind Pegloticase + MTX period or terminate early from the trial.

The final analysis will be conducted after all participants have completed the trial.

Safety data will be reviewed periodically throughout the trial. Safety reviews prior to the primary analysis will be reviewed in a blinded manner.

9.5 Sample Size Determination

A sample size of approximately 240 (120 participants per treatment group) is planned to demonstrate the non-inferiority of the pegloticase 16 mg Q4W + MTX co-administration group compared with the pegloticase 8 mg Q2W + MTX co-administration group (i.e., the active-controlled group in this trial). With a non-inferiority margin set at 20%, this sample size achieves 90% power, assuming a responder rate of 65% in both groups at the 1-sided Type I error rate of 0.025.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical and Trial Oversight Considerations

10.1.1 Sponsor Contact for SAE Reporting

This appendix provides 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. Names and contact information for the Medical Monitor and Sponsor Representative will be filed in the Trial Binder at site.

Sponsor Contact

for SAE Reporting

Horizon Therapeutics U.S.A., Inc.
Fax number for US-based sites: 1-800-860-7836
Email: clinicalsafty@horizontherapeutics.com

24-hour Phone Contact

for Safety Coverage

Med Communications
Phone number: 855-479-6742

10.1.2 Institutional Review Board/Independent Ethics Committee

The Principal Investigator (Investigator), Sponsor and/or designee authorized by the Sponsor will submit this protocol, any protocol modifications, the ICF and all applicable trial documentation to be used in this trial to the appropriate IRB for review and approval/favorable opinion. A letter confirming the IRB approval/favorable opinion of the protocol, the participant 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 participants 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.

10.1.3 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 Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Tripartite Guideline for GCP or with local law if it affords greater protection to the participant. 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."

10.1.4 Participant 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 participant 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 participants are completely free to refuse to enter the trial or to withdraw from it at any time, for any reason. A copy of the signed ICF(s) must be provided to the participant.

The ICF and any other written information provided to participants will be revised whenever important new information becomes available that may be relevant to the participant's consent, or there is an amendment to the protocol that necessitates a change to the content of participant information and/or the written ICF. The Investigator will inform the participant of changes in a timely manner and will ask the participant 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 participant's notes/files of the medical institution.

The eCRFs for this trial contain a section for documenting all participant 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 participants (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. A copy of all signed ICF(s) must be provided to the participant.

10.1.5 Biological Specimens and Data

Trial data and samples are protected by the use of a participant ID number, which is a number specific to the participant. The Investigator is in control of the information that is needed to connect a trial sample to a participant. A participant may withdraw consent to collect samples or personal health data at any time by notifying the Investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the Sponsor, but no new personal health data or samples will be collected unless specifically required to monitor the safety of the participant. If consent is withdrawn the Sponsor is not required to destroy information or data already collected. The Sponsor may store samples for up to 15 years after the end of the trial to achieve trial specified objectives.

10.1.6 Compensation for Health Damage of Participants/Insurance

The Sponsor maintains clinical trial insurance coverage for this trial in accordance with the laws and regulations of the US.

10.1.7 Confidentiality

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

Participant names will not be supplied to the Sponsor. Only the participant number will be recorded in the eCRF, and if the participant's name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Trial findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, participants 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 participant's identity will remain confidential.

The Investigator will maintain a list to enable participants 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.

10.1.8 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 Section 10.1.1 for details). The Sponsor will be responsible for timely reporting of 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 70 sites in the US. Prior to initiation of the trial, each Investigator will provide the Sponsor or its designee a fully executed and signed FDA Form 1572 (or equivalent) 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 3 lists other organizations critical to the conduct of the trial.

Table 3 Table of Non-Sponsor Trial Responsibilities

Contract research organization	Parexel International (IRL) Limited 70 Sir John Rogerson's Quay Dublin 2, Ireland
Clinical drug supply and distribution	PCI Pharma Services 4545 Assembly Drive Rockford, IL 61109
Central safety laboratory	LabCorp Central Laboratory Services 8211 SciCor Drive Indianapolis, IN 46214
Data management	Medidata 350 Hudson Street, 9th Floor New York, NY 10014
Central imaging vendor	Clario 211 Carnegie Center Drive Princeton, NJ 08540
Adjudication services	WCG 212 Carnegie Center Drive. #301 Princeton, NJ 08540
Interactive response technology system	Suvoda 181 Washington Street, Suite 100 Conshohocken, PA 19428

10.1.9 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) participant clinical source documents that corroborate data collected in the eCRFs. Participant clinical source documents include, as applicable, original hospital/clinic participant records; physicians' and nurses' notes; appointment book; original laboratory, ECG, electroencephalogram, radiology, pathology and special assessment reports; dispensing records; signed ICFs; consultant letters; and participant screening and enrollment logs. Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

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 site:

- Medical history/physical condition and diagnosis of the participant before involvement in the trial sufficient to verify that the participant meets protocol entry criteria
- Trial number, assigned participant number and verification that written informed consent(s) was(were) obtained (each recorded in dated and signed progress notes)
- Progress notes or equivalent source documentation for each participant visit and contact (each dated and signed)
- Records of each trial visit including each trial assessment and the identity of the staff member performing the assessment

- IP dispensing and return
- Review by the Investigator or qualified personnel on the 1572 of laboratory test results
- AEs (start and stop dates, description, action taken and resolution)
- Investigator or sub-Investigator's signed assessment of each AE
- Concomitant medications (start and stop dates, reason for use)
- Condition of participant upon completion of, or premature withdrawal from, the trial

10.1.10 Case Report Forms

An eCRF is required for every participant who signs an 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.

10.1.11 Trial Monitoring

The Investigator will ensure that the trial is conducted in accordance with all regulations governing the protection of human participants and will adhere to the basic principles of GCP 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 site 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 participant enrollment, the site 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 participants 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 US 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.

Quality tolerance limits (QTLs) will be predefined in the Quality Plan for the trial to identify systematic issues that can impact participant safety and/or reliability of trial results. These predefined parameters will be monitored during the trial, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical trial report.

Every effort will be made to maintain the anonymity and confidentiality of participants in this trial. However, 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 participants enrolled in this trial. A statement to this effect should be included in the ICF.

10.1.12 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 AEs, medical history and concomitant medication terms will be performed by a qualified medical coder and reviewed and approved by the Sponsor. Concomitant medications will be coded using the World Health Organization Drug Dictionary and AE/medical history/surgery/non-drug therapy terms will be coded using the Medical Dictionary for Regulatory Activities.

10.1.13 Retention of Records

No trial documents at the site should be destroyed without prior written agreement between the Sponsor and the Investigator. All participant 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 or as required by local law following the date of the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in any other ICH region. If an application is not filed or not approved for the indication under study, all trial-related files must be retained for at least 2 years and for a period in compliance with all federal, state and local regulations. The Sponsor must be notified prior to the disposal of any trial-related files. If the Investigator leaves the practice or institution during

the required retention period, it is important that arrangements be made for continued record retention. In that event, the records generally will be retained at the institution at which the trial was conducted.

10.1.14 Publication

The publication policy will be addressed in the Research and Financial Agreement, and all details outlined in the agreement will apply to this protocol. The trial will be registered on ClinicalTrials.Gov prior to the first participant being dosed.

10.2 Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

10.2.1 Definition of AE

AE Definition

As defined by ICH, an AE is any untoward medical occurrence in a clinical trial participant administered a medicinal (investigational or non-investigational) product, whether or not the event is considered related to the medicinal product. 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 medicinal product. 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 IP 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, which should be recorded as medical history.
- Medical or surgical procedures (e.g., endoscopy, appendectomy; however, a condition that leads to a procedure is an AE if it qualifies according to the definitions above).
- Situations in which 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 of “serious” and “non-serious.” This determines the procedures that must be used to report/document the AE.

Unexpected AE 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.

10.2.2 Definition of SAE

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 participant 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 participant 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 an SAE and not resulting in hospital admission does not qualify for this category, but may be appropriately considered a medically important event (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 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 that 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 participant 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, convulsions that do not result in hospitalization and development of drug dependency or drug abuse. If in doubt as to whether an event qualifies as an 'important medical event,' consult the Sponsor's Medical Monitor.

10.2.3 Documentation and Follow-up of AEs and/or SAEs

AE and SAE Documentation

AE and SAE monitoring will begin from signing of the ICF until the 3-month Post-treatment Follow-up Visit.

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

Assessment of Intensity

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 drugs
- Grade 2 (moderate) – symptomatic, duration 1 to 2 weeks, alter lifestyle occasionally, medications give relief (may be prescription), IP continued
- Grade 3 (severe) – prolonged symptoms, reversible, major functional impairment, prescription medications/partial relief, hospitalized < 24 hours, temporary IP discontinuation or/and dose reduced
- Grade 4 (includes life-threatening) – at risk of death, substantial disability, especially if permanent, hospitalized > 24 hours, permanent IP discontinuation

Assessment of Causality

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.

10.2.4 Review of AEs and Emerging New Safety Information

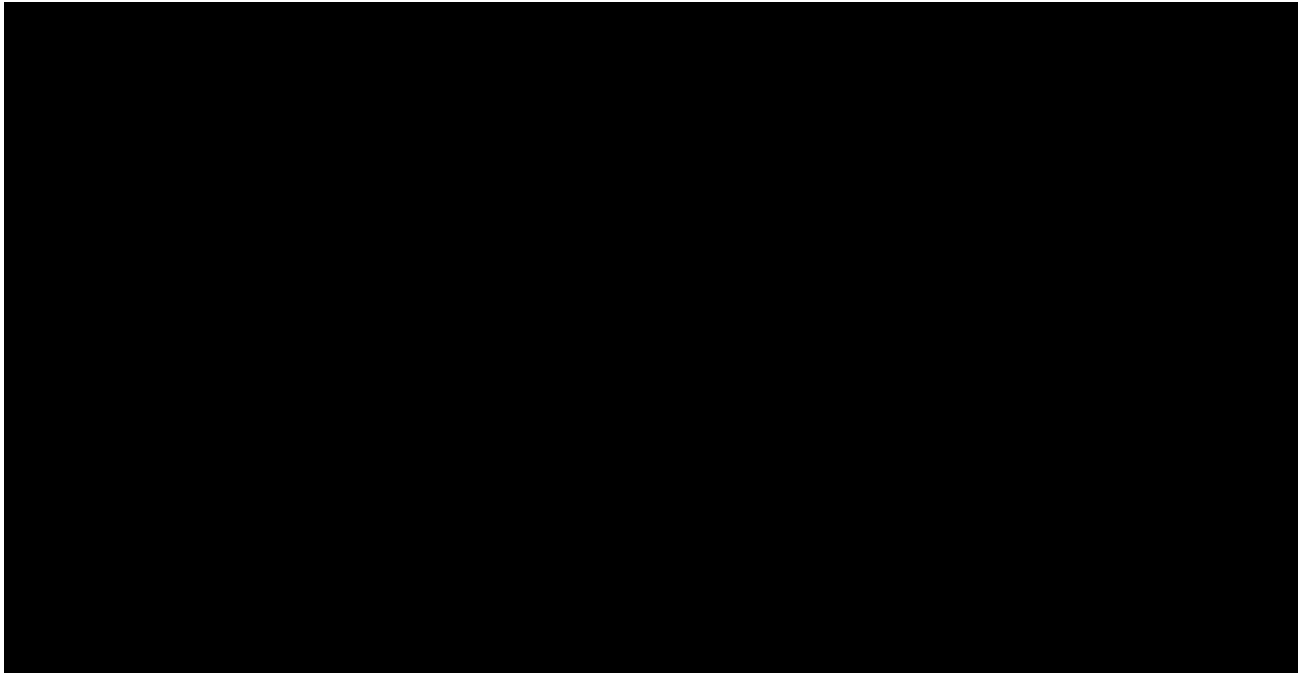
The Sponsor will notify all Investigators involved in the clinical investigation of important safety information regarding the trial treatment, as required by the applicable regulations. Investigators will notify their IRB of all such notifications, as required.

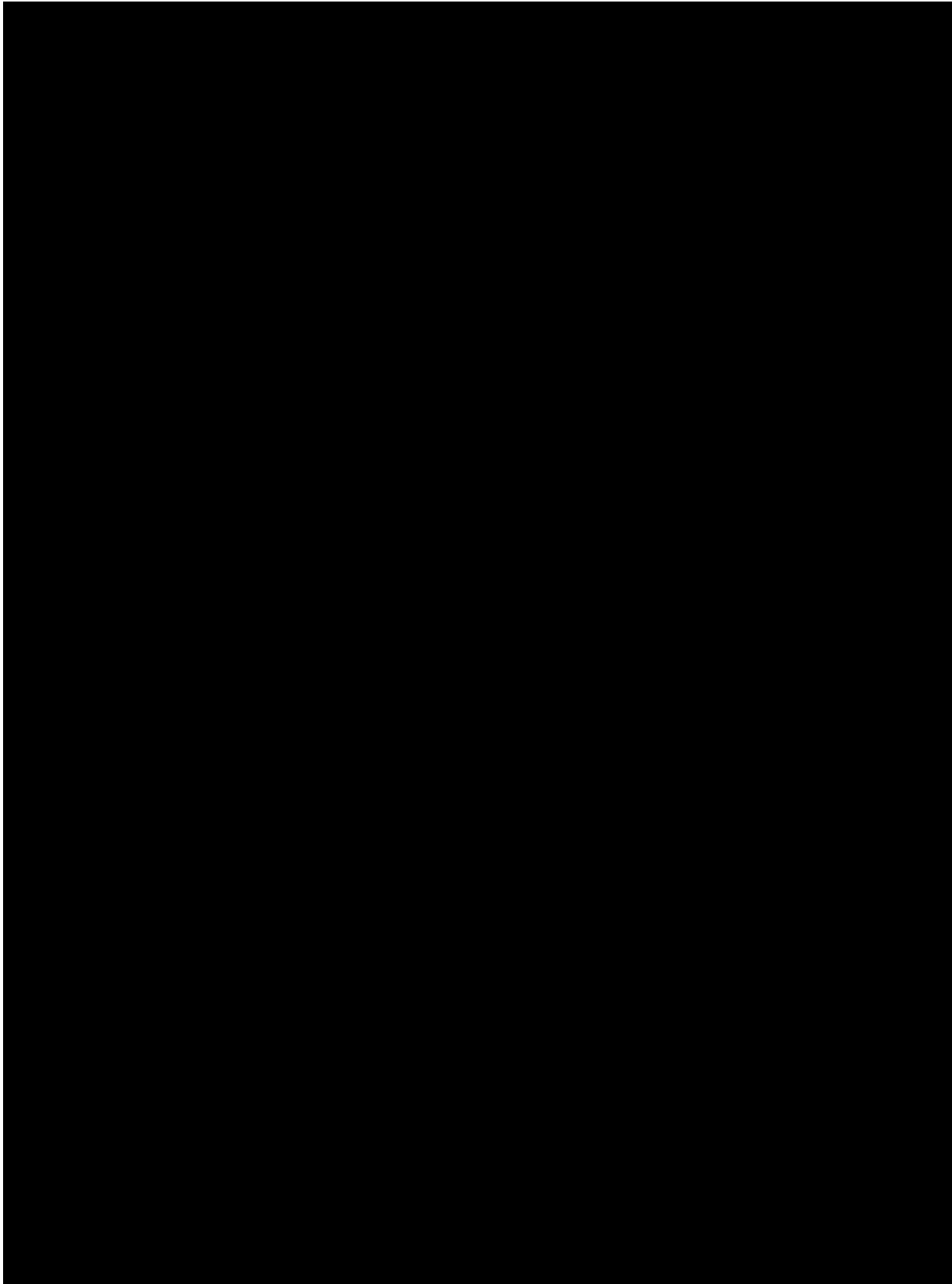
10.2.5 Reporting of IND Safety Reports

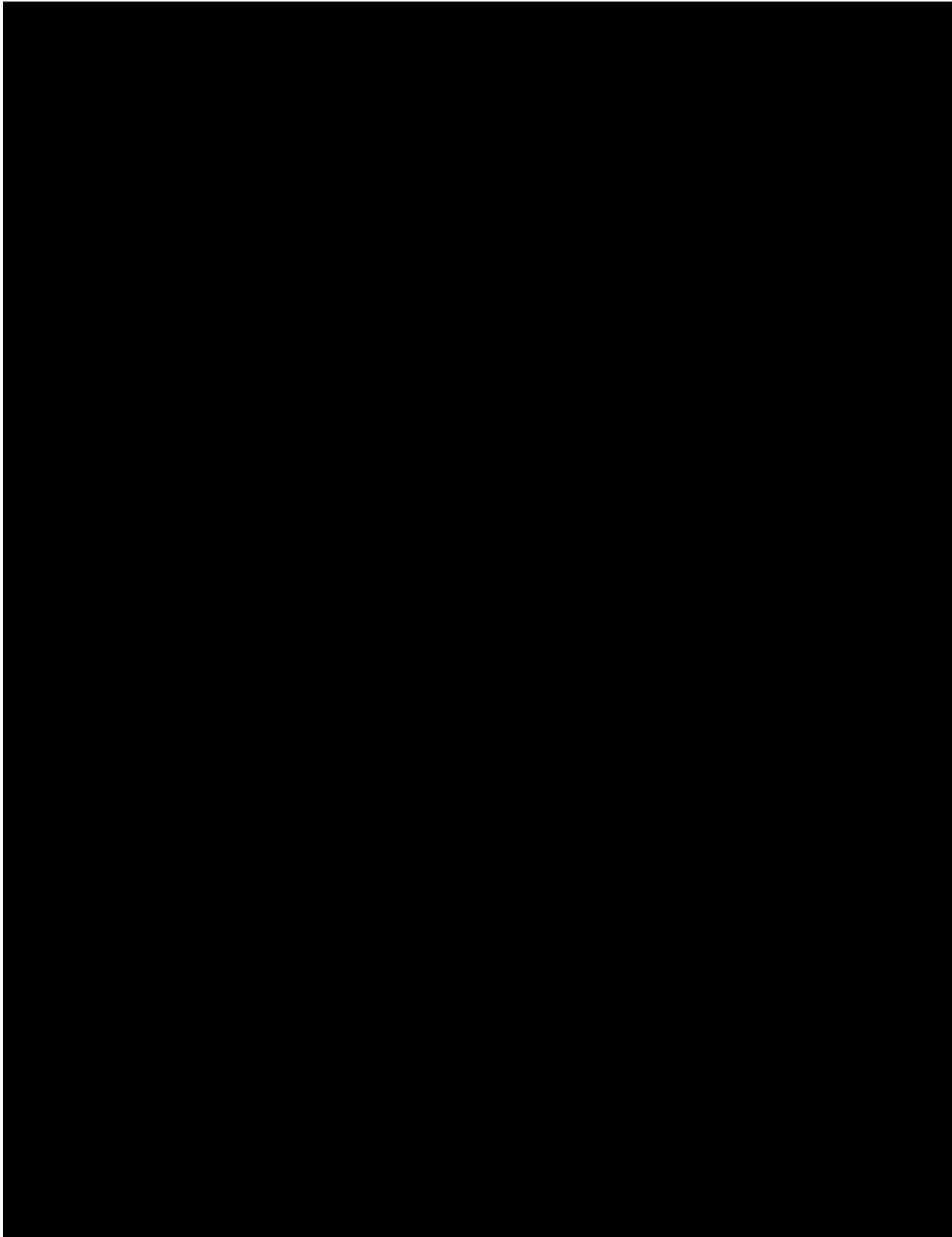
The Sponsor will notify the US FDA and all Investigators on any new serious risks associated with the IPs.

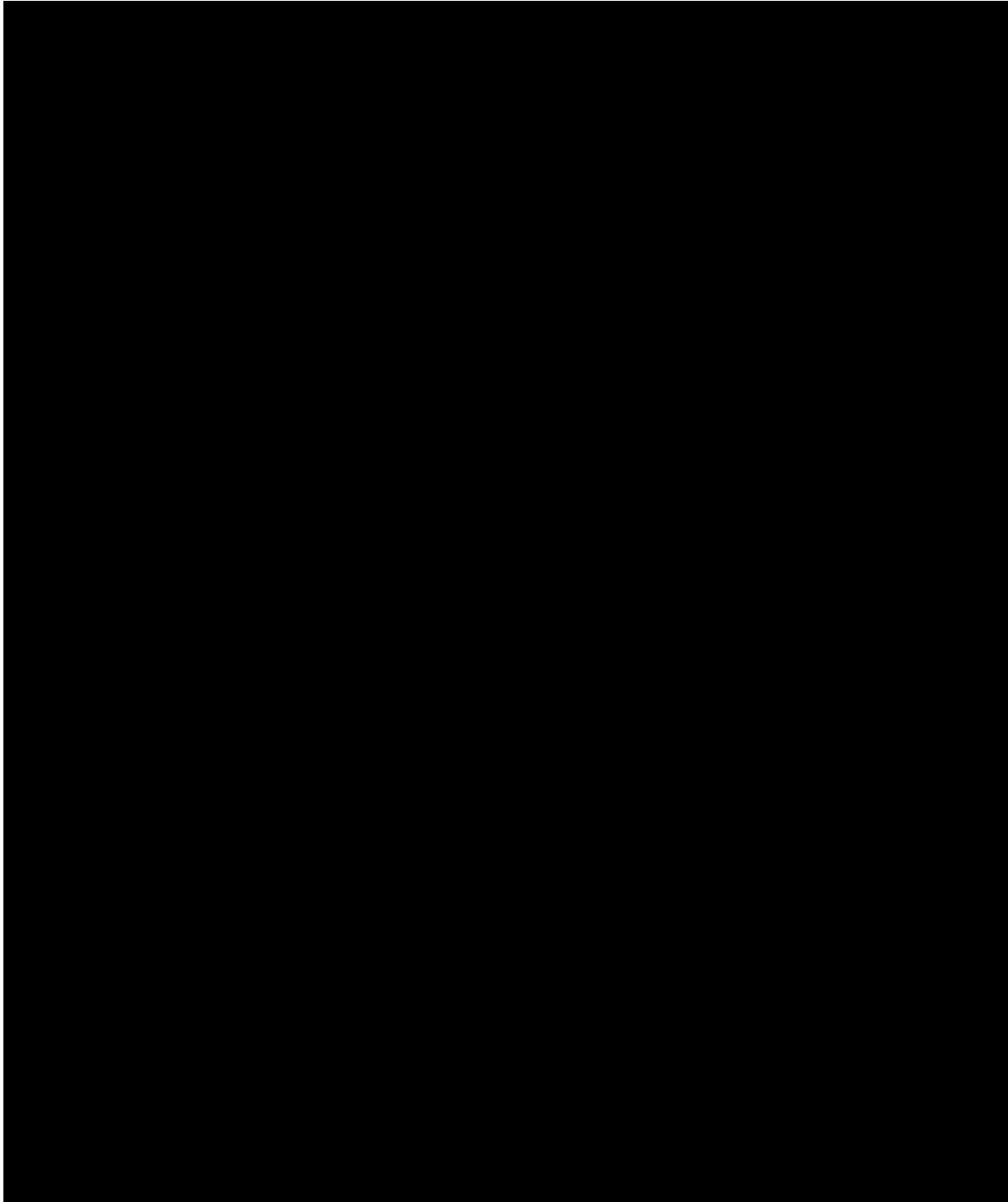
10.2.6 Development Safety Update Reports

The Sponsor or designee will prepare and submit annual safety reports to competent authorities and concerned ethics committees.









11 REFERENCES

AAC Briefing Document, 2009

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].

Brook et al, 2010

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. doi:10.1185/03007995.2010.533647.

Fitzgerald et al, 2020

FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Care Res.* 2020;72(6):744-60. doi:10.1002/acr.24180.

Gaffo et al, 2012

Gaffo AL, Schumacher RH, Saag KG, Taylor WJ, Dinnella J, Outman R, et al. Developing a provisional definition of flare in patients with established gout. *Arthritis Rheum.* 2012;64(5):1508-17. doi:10.1002/art.33483.

Khanna et al, 2016

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. doi:10.1080/00325481.2016.1113840.

KRYSTEXXA

KRYSTEXXA (pegloticase injection). Full Prescribing Information. Horizon Therapeutics USA, Deerfield, IL, USA; Approval 2022. Available at: <https://www.hzndocs.com/KRYSTEXXA-Prescribing-Information.pdf>

Mikuls et al, 2005

Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR Jr, Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990-1999. *Ann Rheum Dis.* 2005;64(2):267-72. doi:10.1136/ard.2004.024091.

Roddy and Doherty, 2010

Roddy E, Doherty M. Epidemiology of gout. *Arthritis Res Ther*. 2010;12(6):223. doi:10.1186/ar3199.

Saag and Choi, 2006

Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. *Arthritis Res Ther*. 2006;8 Suppl 1:S2. doi:10.1186/ar1907.

Sampson et al, 2006

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, 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. doi:10.1016/j.jaci.2005.12.1303.

Sattui et al, 2014

Sattui SE, Singh JA, Gaffo AL. Comorbidities in patients with crystal diseases and hyperuricemia. *Rheum Dis Clin North Am*. 2014;40(2):251-78. doi:10.1016/j.rdc.2014.01.005.

Singh and Strand, 2008

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. doi:10.1136/ard.2007.081604.

Strand et al, 2017

Strand V, Balsa A, Al-Saleh J, Barile-Fabris L, Horiuchi T, Takeuchi T, et al. Immunogenicity of biologics in chronic inflammatory diseases: a systematic review. *BioDrugs*. 2017;31(4):299-316. doi:10.1007/s40259-017-0231-8.

Wertheimer et al, 2013

Wertheimer A, Morlock R, Becker MA. A revised estimate of the burden of illness of gout. *Curr Ther Res Clin Exp*. 2013;75:1-4. doi:10.1016/j.curtheres.2013.04.003.

Woodworth et al, 2007

Woodworth T, Furst DE, Alten R, Bingham CO, Yocum D, Sloan V, 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.

Ye et al, 2023

Ye T, Bannick M, Yi Y, Shao J. Robust Variance Estimation for Covariate-Adjusted Unconditional Treatment Effect in Randomized Clinical Trials with Binary Outcomes. *Stat Theory Relat Fields*. 2023;7(2):159-163. doi: 10.1080/24754269.2023.2205802. Epub 2023 Apr 28. PMID: 37997606; PMCID: PMC10665030.

Zhu et al, 2011

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. doi:10.1002/art.30520.