Statistical Analysis Plan

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

Prepared for:

Horizon Therapeutics Ireland DAC

Protocol Number: HZNP-KRY-403 (Version 5.0, Amendment 4)

SAP Version 2.0 Final

Date: 19 Jan 2024

REVISION HISTORY

Version	Date	Revision Author	Comments
Final v2.0	19Jan2024	[redacted]	• Updates per protocol Version 5 amendments • Updates to text, including the title, to match protocol updates. • Moved [redacted] rate from an exploratory objective to a secondary objective and clarified details of analysis • Moved all safety objectives under the secondary objectives to the safety objectives • Added exploratory objectives [redacted] • Sample size updated to approximately 110 for the selected cohort • Deleted handling the COVID-19 discontinuation in efficacy analysis. • Laboratory data and vital sign summaries updated to include results from within 30 days (inclusive) from the later one of the last dose of pegloticase or MTX • Added analysis of exposure adjusted incidence rate for select AE summaries • Estimand language added for primary and secondary endpoints. Analysis clarifications added throughout. • Summaries of response and IR by ADA status added

A PHASE 4, MULTICENTER, OPEN-LABEL, INFUSION DURATION STUDY TO ASSESS SAFETY, TOLERABILITY AND EFFICACY OF PEGLOTICASE ADMINISTERED WITH A SHORTER INFUSION DURATION IN SUBJECTS WITH UNCONTROLLED GOUT RECEIVING METHOTREXATE (HZNP-KRY-403)

SPONSOR SIGNATURE PAGE

DocuSigned by:
[redacted]
Signer Name: [redacted]
Reason: I am the author of this document
Signing Time: 19-Jan-2024 | 17:30 CST
A1B826E5414D483F8E08CB3A12F33DB4

19-Jan-2024 | 17:30 CST
Date

[redacted], MS
Study Biostatistician, Rare Disease

DocuSigned by:
[redacted]
Signer Name: [redacted]
Reason: I approve this document
Signing Time: 19-Jan-2024 | 16:16 CST
220256595FE94748938D9D7EA8DA426E

19-Jan-2024 | 16:17 CST
Date

[redacted], MD
Director, Biostatistics, Rare Disease

DocuSigned by:
[redacted]
Signer Name: [redacted]
Reason: I approve this document
Signing Time: 22-Jan-2024 | 00:13 CST
9B097010E26D4586A9BD98BA31B78658

22-Jan-2024 | 00:13 CST
Date

[redacted], MD
Sr. Medical Director, Rare Disease

TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
BLQ	below limit of quantification
BP	blood pressure
CI	confidence interval
CM	concomitant medication
CNS	central nervous system
CSR	clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IR	infusion reaction
ITT	intent-to-treat
KM	Kaplan-meier
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
mITT	modified intention-to-treat
OC	observed cases
PEG	polyethylene glycol
PK	pharmacokinetics
PT	preferred term
PY	person years
SAP	statistical analysis plan
SD	standard deviation
SMQ	standardised MedDRA queries
SOC	system organ class
sUA	serum uric acid

TEAE	treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

1 Study Information

1.1 Background

This statistical analysis plan (SAP) describes the analysis variables and statistical procedures that will be used to analyze and report the results from the Protocol of HZNP-KRY-403 version 5.0 (amendment 4) dated Nov 09, 2022.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports".

1.1.1 Study Objectives

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

Primary Objective

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

Secondary Objectives

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

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

Exploratory Objectives

- Assess the pharmacokinetics (PK) of pegloticase.
- Assess the profile of anti-uricase antibodies and anti-polyethylene glycol (PEG) antibodies.

Safety Objectives

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

1.1.2 Study Design

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

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

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

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

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

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

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

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

Prior to the Pegloticase + MTX Period, subjects will begin taking at least one of the per protocol standard gout flare prophylaxis regimen (colchicine 0.6 mg/day and/or nonsteroidal anti-inflammatory drug (NSAID) and/or low dose prednisone <10 mg/day) for ≥1 week before the first dose of pegloticase and continues flare prophylaxis throughout the pegloticase treatment period per American College of Rheumatology guidelines [FitzGerald JD et al. 2020].

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

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

Up to three pegloticase infusion durations will be assessed in the Pegloticase + MTX Period: 60-minute infusion, 45-minute infusion and 30-minute infusion. Cohorts of approximately 10 subjects will be enrolled sequentially at progressively shorter infusion durations initially, beginning with the 60-minute infusion duration, progressing down to the 45-minute infusion duration and then to the 30-minute infusion duration. If deemed safe, enrollment will continue until approximately 110 subjects are enrolled (e.g. 110 subjects in the 30-minute infusion cohort, unless 30-minute infusion was not tolerated and then up to approximately 110 subjects may be enrolled in the 45-minute or 60-minute infusion cohort). The most desirable infusion duration is the shortest duration which is shown to be safe and well tolerated. Safety will be continuously monitored, and if any safety concerns are identified in any of the given enrollment infusion duration cohorts, screening/enrollment may be paused until safety data is evaluated by the Safety Review Committee (SRC) and/or restarted at the same or another infusion duration.

After the first 3 subjects at each infusion duration complete at least 4 weeks of the Pegloticase + MTX Period (3 infusion visits), a holistic safety assessment will be performed by the internal SRC on available subjects' data. Study enrollment will not be paused during this safety assessment. If a subject discontinues treatment or study prior to the third infusion visit, their available data is still included in the safety assessment. If the safety assessment indicates that the infusion duration is well tolerated (based on pre-determined infusion speed-limiting criteria as described in protocol section 9.2), then additional safety assessments will continue to be performed based on available subjects' data after 6 subjects and 10 subjects complete at least 4 weeks of the Pegloticase + MTX period (3 infusion visits). Enrollment will be paused after the 10^{th} subject of each infusion duration cohort is enrolled until after the 4-week (3-infusion visits) safety assessment analysis results are known and reviewed by the SRC.

If the SRC determines that it is safe to proceed to the next progressively shorter infusion duration, subjects who are already enrolled may continue at the same infusion duration or modify infusion duration based on Investigator's discretion.

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

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

The SRC can increase the number of subjects at the chosen infusion duration level to up to 110 subjects.

Investigators will be permitted to adjust the duration of the infusion at a particular infusion visit regardless of initial treatment duration assignment, if needed. The decision to modify the

infusion duration at a visit will be allowed based on the investigator's discretion. Subjects may return to the original infusion duration for subsequent infusions.

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

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

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.

Adverse events of special interest (AESIs) defined in the protocol are gout, IRs, anaphylaxis and cardiovascular events. All AESIs except gout flare will be adjudicated by a team of external experts with experience in immunology, allergic reactions, rheumatology and/or cardiovascular diseases.

1.1.3 Determination of Sample Size

Approximately 10 subjects will be enrolled sequentially at progressively shorter infusion durations, beginning with the 60-minute infusion duration, progressing down to the 45-minute infusion duration and then to the 30-minute infusion duration. Approximately 110 subjects are planned to be enrolled into a desirable infusion cohort that does not meet the dose limiting criteria. Therefore, the total number of subjects enrolling across the 3 different cohorts in the study is approximately 130.

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

1.2 Efficacy Assessments

1.2.1 Serum Uric Acid

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

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

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

1.3 Safety Assessments

Safety will be assessed via AE and concomitant medication (CM) use monitoring, physical examinations, vital signs, clinical safety laboratory evaluations (hematology, chemistry, urine albumin: creatinine ratio), pregnancy testing (if applicable), ECGs and AESIs (i.e., IRs, anaphylaxis, gout flares and cardiovascular events).

All adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 23.0). Medications will be coded using World Health Organization Drug Dictionary (WHO-DD Global B3 March 2020).

AESIs defined in the protocol for adjudication (See protocol Section 9.6.1.2.1.5) are IRs, anaphylaxis and cardiovascular events. These will be adjudicated by an external committee of subject matter experts. The AESI of gout flare will not be adjudicated.

1.4 Pharmacokinetic and Anti-drug Antibody Measurements

1.4.1 Pegloticase Pharmacokinetics

For all subjects, serum samples for pegloticase PK analysis will be collected approximately 15 minutes to 2 hours after the end of infusion on Day 1; prior to infusion and approximately 15 minutes to 2 hours after the end of the infusion at Weeks 2, 6, 12 and 20. An additional PK sample will be collected at the End-of-Study (Week 24)/Early Termination Visit.

1.4.2 Anti-drug Antibody (ADA) Measurements

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

1.4.3 MTX Polyglutamate Measurements

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

1.5 Endpoints

1.5.1 Primary Endpoint

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

1.5.2 Secondary Endpoints

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

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

1.5.3 Exploratory Endpoints

[redacted]

1.5.4 Safety Endpoints

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

1.5.5 Pharmacokinetic and Anti-drug Antibody Endpoints

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

1.6 Treatment Periods

- MTX Run-in Period
    - For summaries by study visit, only includes Week -4 and Week -2 study visits

- For assignment of study period to ongoing assessments (e.g. AE or CM), includes all activities from the date and time of first MTX dose to the date and time of the first dose of pegloticase.

- Pegloticase + MTX Period
  - For summaries by study visit, includes all visits starting with Day 1 through Week 24 and/or End of Pegloticase visit
  - For assignment of study period to ongoing assessments (e.g. AE or CM), includes all activities from the date and time of the first dose of pegloticase to the date of the Week 24 and/or End of Pegloticase visit

2 Analysis Sets

The statistical analyses will be performed based on the following analysis sets:

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

3 Statistical Methods

3.1 General Methods

Any changes to the finalized SAP made prior to database lock will be documented in an SAP amendment. Any changes to the planned analyses after database lock will be documented in the clinical study report (CSR).

Some of the analyses detailed here may be more explicit or in some aspects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

3.1.1 Reporting Conventions

The formats for the tables, listings, and figures described in this SAP will be provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the CSR.

Study data from the electronic case report forms as well as relevant derived variables will be provided in subject data listings. An indication of specific listings for each data type may be indicated in the text of subsequent SAP sections. Data listings supplied as part of the CSR will be sorted by study center number concatenated with subject number, assessment dates, and time point, if collected.

The following conventions will be applied to all data presentations and analyses:

Continuous variables will generally be summarized by the number of subjects, mean, standard deviation, median, minimum, and maximum. Unless otherwise specified, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data

Categorical variables will be summarized using frequencies and percentages within each category. Unless otherwise specified, the percentage will be presented in parentheses to one decimal place. Frequency and percentage values of 0 will be presented as '0' rather than '0 (0)'.

Unless otherwise specified, time to event data will be reporting using weeks as the timescale.

All summary tables will include the analysis set sample size (i.e., number of subjects).

Date variables will be formatted as DDMMMYYYY for presentation.

Unless otherwise specified, confidence intervals (CI) will be based on two-sided 95% confidence.

If multiple assessments occur at a given post-baseline time point, the latest value will be used.

There will be no statistical testing to make an inference.

3.1.2 Treatment Groups for Data Summaries

Unless otherwise specified, analyses using the ITT analysis set will be restricted to the MTX Run-in Period and will be presented as one treatment group called "MTX".

The mITT analysis set will be used for the analysis of efficacy endpoints [redacted] and will be presented by "as-assigned" infusion duration group. Summaries will be categorized based on the infusion duration assigned at Day 1 visit.

PK and ADA endpoints will be analyzed by "as assigned" infusion duration group for the PK analysis set. MTX polyglutamate analyses will be presented by "as assigned" infusion duration group using the mITT analysis set. Remaining primary, secondary, exploratory, and safety endpoints analyses will be summarized for the safety analysis set and will be presented by "as-assigned" treatment group.

Select safety analyses may also be summarized by "as-treated" group if at least 3 subjects in an assigned infusion duration group receive an infusion at a duration that differs from their assigned duration. Given the possibility of subjects switching from the assigned duration to other durations, subjects will fall into a specific treatment duration group (i.e. column header N) if they

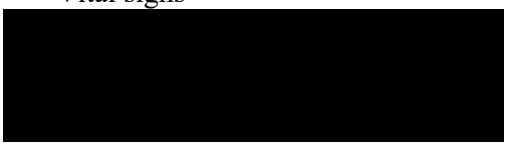
have at least one infusion done at the indicated infusion duration. If a subject is treated with more than one infusion duration, then that subject will be counted in both infusion duration groups' denominator. Results corresponding to the infusion subjects actually take at any moment in the study will be windowed based on start date and time of each treatment and summarized in the corresponding treatment group category. One subject's results may appear in multiple treatment categories depending on what treatment was taken at each point in the study. Additional details on windowing for determination of actual treatment status for a specific result are described in Treatment Windowing (Section 3.1.5).

Data for the Pegloticase + MTX Period will be summarized descriptively by infusion duration regimen as described above, unless otherwise specified. In other words, analyses of the mITT or safety analysis sets in any period will be presented by infusion duration group: "60-Min Pegloticase + MTX", "45-Min Pegloticase + MTX", "30-Min Pegloticase + MTX". If other infusion durations > 60 minutes are used in the study, then those will be presented in a separate treatment group: "> 60-Min Pegloticase + MTX" for any analyses done by "as treated" group.

3.1.3 Definition of Baseline

The MTX baseline is defined as the last non-missing observation prior to the first dose of MTX. The following assessments will utilize the MTX baseline when assessing changes from baseline or shift tables within the MTX Run-in Period and the Pegloticase + MTX Period:

- Vital signs



- Hematology and chemistry laboratory parameters

The pegloticase baseline is defined as the last non-missing observation prior to the first dose of pegloticase. The following assessments will use the pegloticase baseline when assessing changes from baseline or shift tables within the Pegloticase + MTX Period:

- Vital signs

- MTX polyglutamate
- Pegloticase PK
- Urine albumin: creatinine ratio
- Antibody
- Hematology and chemistry laboratory parameters

Change from baseline for a time period will be calculated as the value at the time point of interest minus the appropriate baseline value for that time period.

3.1.4 Study Day

Two different study days will be calculated. The first study day (MTX study day) will be determined relative to the first dose of MTX in the MTX Period. The second study day (Pegloticase study day) will be determined relative to the first infusion of pegloticase.

For both study day calculations, for study days on or after the first dose date the study day will be calculated as assessment date – first dose date + 1. For study days prior to the first dose date, study day will be calculated as assessment date – first dose date. Therefore, there will be no study day 0.

3.1.5 Visit Windowing

For all analyses, data will be summarized according to the scheduled visit and time points as outlined in the protocol and by the visit denoted on the electronic case report form (eCRF). The reference date associated with each visit is collected on the Visit Date eCRF page. Further, the End of Study/Early Termination (ET) visit and the End of Pegloticase Infusion Visit will be windowed to a visit based on the study day of occurrence relative to the target day of each scheduled visit according to Tables 1-8 below.

Table 1: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (Vital Signs, sUA)

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 2	15	2 – 22
	Week 4	29	23 – 36
	Week 6	43	37 – 50
	Week 8	57	51 – 64
	Week 10	71	65 – 78
	Week 12	85	79 - 92
	Week 14	99	93 – 106
	Week 16	113	107 – 120
	Week 18	127	121 – 134
	Week 20	141	135 – 148
	Week 22	155	149 – 162
	Week 24	169	≥ 163

[a] Study days in the Pegloticase + MTX Period will be calculated relative to the first dose of Pegloticase.

Table 2: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (Laboratory Assessments and Urine Albumin: Creatinine Ratio)

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 2	15	2 – 29
	Week 6	43	30 – 71
	Week 14	99	72 – 127
	Week 22	155	128 – 162
	Week 24	169	≥ 163

[a] Study days in the Pegloticase + MTX Period will be calculated relative to the first dose of Pegloticase.

Table 3: Visit Windows for Assigning ET and End of Pegloticase Visits to a Scheduled Visit (Pegloticase PK and Antibody testing)

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 2	15	2 – 29
	Week 6	43	30 – 64
	Week 12	85	65 – 113
	Week 20	141	114 – 155
	Week 24	169	≥156

[a] Study days in the Pegloticase + MTX Period will be calculated relative to the first dose of Pegloticase.

Table 4: Visit Windows for Assigning ET and End of Pegloticase Visits to a Scheduled Visit (Pre-infusion MTX Polyglutamate PK)

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 14	99	2 – 127
	Week 22	155	128 – 162
	Week 24	169	≥163

In the event that an End of Study/ET or End of Pegloticase visit is reassigned to a visit for which the subject has scheduled data collected, the data from the nominal scheduled visit will take precedence and the data from the End of Study/ET or End of Pegloticase visit will not be summarized. If the End of Study/ET or End of Pegloticase visit maps to a visit where the assessment was scheduled to be collected, and a scheduled collection is not available at that time point, the End of Study/ET or End of Pegloticase visit data will be summarized in the scheduled visit assessment.

3.1.6 Treatment Windowing for "As-Treated" Summaries

This section describes how treatment (infusion duration) will be assigned to study results for "as-treated" summaries (if warranted) and for AE listings, using the safety analysis set.

Results collected at a particular study visit:

- Results in the MTX Run-in Period and for Day 1 should always be corresponding to the assigned treatment group.
- Pre-infusion results after Day 1 should correspond to the treatment given at the prior visit. For example, if a subject took 60-min infusion at Day 1, but then attended their Week 2 visit and had a 120-min infusion done, then their Week 2 pre-infusion results would correspond to the 60-min treatment group and their Week 4 visits would correspond to the >60-min treatment group.
- Post-infusion results should correspond to the actual treatment given at the visit. E.g. using the same example as above, if 120-min infusion was given at Week 2, then post-infusion results should correspond to > 60-min treatment group.
- Results at Week 24 and at end of pegloticase infusion should correspond to the last treatment that a subject took.
- Follow-up results will correspond to the last treatment that a subject took.

3.1.7 Handling Rules for sUA Values

For the determination of sUA responder endpoints, scheduled assessments of sUA and unscheduled assessments of sUA, reported by the central laboratory, will be used. Local

laboratory-processed pre-infusion sUA results will be used only when the central laboratory-processed value at a time point is not available, but the local lab-processed pre-infusion value, collected value at the same time point, is available.

When the central laboratory or local laboratory reports a value for sUA as being lower than or lower than and equal to the lab assay's limit of quantification (e.g. "<0.02" or "<= 0.02"), zero will be used as the numeric value for the purpose of determining response and for summaries of observed values and the change from baseline. When the central laboratory or local laboratory reports a value for sUA as being higher than or higher and equal to a certain value of quantification (e.g. ">8.7", ">= 8.7"), the numeric value (e.g. 8.7) after '>' or ">=" is used for the purpose of determining response and for summaries of observed values and the change from baseline

Unscheduled sUA visits, assessed by the central laboratory or local laboratory, will be assigned an analysis window according to the tables above in Visit Windowing (Section 3.1.5-). These unscheduled visits will be used for the determination of sUA responder.

3.1.8 Pooling of Centers

Data from sites will be summarized together for analyses

3.2 Handling of Missing Data

Aside from responder rates, where non-responder imputation is planned (see Exploratory Endpoints, Section 3.4.3), summary statistics will be computed for each efficacy endpoint using the Observed Cases (OC) with no imputation for missing data.

Unless otherwise specified, no other imputation of missing values will be done.

3.2.1 Medication Dates

For prior and concomitant medications with incomplete dates, the following rules will be used to impute start and/or stop dates for the purposes of determining if a medication is prior, concomitant in the MTX Run-in Period, or concomitant in the Pegloticase + MTX Period. Imputed dates will not be presented in the data listings.

For partial start dates:

- If the month and year are provided and day is missing, and the month and year match the month and the year of the first pegloticase dose date AND match the month and the year of the first MTX dose (i.e. the MTX and pegloticase started in the same month), the day of the first dose date of MTX will be imputed. Otherwise, if the month and year match the month and year of the first pegloticase dose date, then the first dose date of pegloticase will be imputed. Otherwise, if the month and year match the month and year of the first MTX dose date, then the first dose date of MTX will be imputed. Otherwise, the first of the month will be used.

- If the year is provided and the month and day are missing and the year matches the year of the first pegloticase dose date and the year matches the year of the first MTX dose date,

the month and day of the first MTX date will be imputed. Otherwise, if the year matches the year of the first dose of pegloticase, the first dose date of pegloticase will be imputed. Otherwise, if the year matches the year of the first MTX date, then the first dose date of MTX will be imputed. Otherwise, January will be used.

- If the start date is completely missing, the start date will not be imputed. If the stop date is after first dose date of pegloticase, the medication will be considered to be both prior, concomitant in the MTX Run-in Period, and concomitant in the Pegloticase + MTX Period. If the stop date is after the first dose date of MTX, but prior to the first dose date of pegloticase, the medication will be considered to be prior and concomitant in the MTX Run-in Period. If the stop date is prior to the first dose date of MTX, the medication will be considered to be prior only.

- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

For partial stop dates:

- If the month and year of stop are provided, but the day is missing, then the last day of the month will be used.

- If the year of stop is provided, but the month and day are missing, then December 31st of that year will be used.

If the stop date is completely missing, then the date of last study visit will be used.

3.2.2 Adverse Events

For adverse events with incomplete dates, the following rules will be used to impute start and/or stop dates for the sole purpose of determining if an AE is treatment-emergent in the MTX Run-in Period or Pegloticase + MTX Period. Imputed dates will not appear in the data listings.

For partial start dates:

- If the month and year of adverse event onset/worsening are provided but day is missing

    - If the month and year match the month and year of the first dose of MTX in the MTX Run-in Period AND match the month and year of the first infusion of pegloticase in the Pegloticase + MTX Period, the first dose date of MTX in the Run-in Period will be imputed and the event will be considered treatment emergent in the MTX Run-in Period and Pegloticase + MTX Period.

    - Otherwise, if the month and year match the month and the year of the first dose date of pegloticase, the day of the first infusion date of pegloticase will be imputed and the AE will be considered treatment-emergent in the Pegloticase + MTX Period.

    - Otherwise, if the month and year match the month and the year of the first dose date of MTX, the day of the first dose date of MTX will be imputed and the AE will be considered treatment-emergent in the MTX Run-in Period.

  - Otherwise, the first of the month will be used and the treatment-emergent status will be assessed relative to the first infusion date of pegloticase and the first dose date of MTX.

- If the year of adverse event onset is provided, but the month and day are missing

  - If the year matches the year of the first dose of MTX in the MTX Run-in Period AND matches the year of the first infusion of pegloticase in the Pegloticase + MTX Period, the first dose date of MTX in the Run-in Period will be imputed and the event will be considered treatment emergent in the MTX Run-in Period and Pegloticase + MTX Period.

  - Otherwise, If the year matches the year of the first infusion date of pegloticase, the month and the day of the first infusion date of pegloticase will be imputed, and the AE will be considered treatment-emergent in the Pegloticase + MTX Period.

  - Otherwise, if the year matches the year of the first dose date of MTX, the month and day of the first dose of MTX will be imputed and the AE will be considered treatment-emergent in the MTX Run-in Period.

  - Otherwise, January 1st will be used and the treatment-emergent status will be assessed relative to the dosing start date of pegloticase and the first dose date of MTX.

- If the start date is completely missing, the AE will be considered treatment-emergent in the Pegloticase + MTX Period and the MTX Run-in Period, unless the stop date is complete or provides enough partial information to rule out a treatment-emergent status in the Treatment Period. This should be a rare occurrence.

- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

Events with missing relationship to study drug in the MTX Run-in period will be considered "related" to Methotrexate for statistical summaries. Events with missing relationship to study drug in the Pegloticase + MTX period will be considered "related" to Methotrexate and "related" to pegloticase for statistical summaries.

Missing severities will be considered "severe" for statistical summaries. Any preferred terms with a missing severity will be described in the table footnotes.

3.3 Study Subjects

3.3.1 Subject Disposition

Subject disposition corresponding to the MTX Run-in Period will be summarized for all subjects combined. Subject disposition corresponding to the Pegloticase + MTX Period will be summarized by assigned infusion duration group and overall.

For disposition summaries corresponding to the MTX Run-in Period, the denominator for percentages corresponding to the subjects who discontinued or completed the MTX Run-in Period and to subjects who entered the Pegloticase + MTX Period will be based on the number of subjects who entered in the MTX Run-in Period. The denominator for all other percentages in the MTX Run-in Period will be based on the number of subjects who were screened.

Disposition for the MTX Run-in Period will include the number and percentage of subjects who:

- Screened
- Overall Screen Failures, with reason (unable to tolerate MTX vs. other)
- Entered the MTX Run-in Period (ITT Set)
- Discontinued from the MTX Run-in Period (MTX screen failure)
- Completed the MTX Run-in Period
- Entered the Pegloticase + MTX Period

For summaries corresponding to the Pegloticase + MTX Period, the number of subjects entering the Pegloticase + MTX Period (mITT analysis set) will be used for the denominator of the percentages. Disposition summaries for the Pegloticase + MTX Period will include the number and percentage of subjects who:

- Are in the mITT, Safety, and the PK analysis sets
- Completed treatment in the Pegloticase + MTX Period
- Discontinued early from treatment in Pegloticase + MTX Period along with reason for discontinuation
- Discontinued early from treatment in the Pegloticase + MTX Period but continued in the study
- Completed the study
- Discontinued early from the study along with reason for early discontinuation

A shift table will also be created to demonstrate any shift subjects had from the original assigned infusion duration to other infusion durations. Shifts will be presented for the last visit in the Pegloticase + MTX Period and by each visit. Denominator for overall shift percentage will be the total number of subjects assigned to each treatment group at Day 1 visit. Denominator for the per-visit shift percentage will be the total number of subjects assigned to each treatment group at Day 1 visit who also attended the indicated visit.

3.3.2 Study Visits

A summary of the number and percentage of subjects attending each visit by treatment period will be provided. The denominator for the MTX Run-in Period will be the number of subjects in

the ITT analysis set; the denominator for the Pegloticase + MTX Period will be the number of subjects in each assigned treatment group in the mITT (equivalently, Safety) analysis set.

3.3.3 Protocol Deviations

All protocol deviations and the reasons for such deviations will be documented in the eCRF. Sites will be issued specific instructions to follow in order to capture missed visits, out of window visits, treatment interruptions and treatment discontinuations due to COVID-19 on the eCRF. Details to be recorded include whether a subject has suspected or confirmed COVID-19 infection and whether the study site is open or closed. Deviations will be categorized by type and as major or minor. In the event of a major protocol deviation, the Investigator and Sponsor's Medical Monitor will determine whether the subject should continue to participate in the study.

All protocol deviations will be provided for the ITT analysis set as a summary by period of occurrence, and by type and in total. Protocol deviations in the screening period and MTX Run-in Period will be summarized for the MTX treatment group. Protocol deviations from the pegloticase + MTX treatment period will be summarized by assigned infusion duration group.

A single listing of all protocol deviations will also be created, including period of occurrence (screening, MTX Run-in, Pegloticase + MTX Period, and Follow-up Period).

3.3.4 Demographic and Baseline Characteristics

Demographic data, including age (years), age category (< 65 years, ≥ 65 years), race, childbearing potential, ethnicity and sex, height (cm), weight (kg) will be summarized for the ITT and mITT analysis sets.

Baseline characteristics, including time since first gout attack and diagnosis (in years), presence of uric acid crystals confirming diagnosis, number of (acute) flares in past 12, 6, and 1 month(s) , pattern of flares, typical severity of flares, chronic gout synovitis/arthropathy status, prior/current tophi, history of overnight hospital stay for gout, history of surgery for gout (excluding arthrocentesis), history of kidney stones, episodes of renal colic (past year), kidney function impact by gout, and urate lowering therapy will be summarized for the ITT and mITT analysis sets using descriptive statistics.

Summaries of demographic and baseline characteristics for the mITT analysis set will be by assigned infusion duration and overall. Listings will include all screened subjects.

Results collected at the screening visit will be used for analysis.

3.3.5 Medical History

Medical history, including surgical history and symptom severity, will be conducted at the screening visit and summarized for the ITT and mITT analysis sets. Medical history events will be summarized overall and by SOC and PT in alphabetical order.

The coding of an AE, medical history and concomitant medication terms will be performed by EMB Statistical Solutions and reviewed and approved by a Horizon Therapeutics Medical Monitor.

3.3.6 Prior and Concomitant Medications and Procedures

Prior medications will include any medications, with a start date prior to (but not including) the start date of MTX dosing. Prior medications (not including gout medications) will be collected for 1 year prior to screening.

Concomitant medications include drug or biological products other than the study drugs (or prior gout medications) taken by a subject after a dose of study drug. This includes other prescription medications (including preventive vaccines), over the counter medications, herbal medications, vitamins and food supplements.

Prior medications, concomitant medications used during the MTX Run-in Period, and concomitant medication used in the Pegloticase + MTX Period will be summarized by presenting the counts and percentage of subjects using medications overall for the ITT and Safety Analysis Sets as appropriate. Summaries will be presented by Anatomical Therapeutic Chemical (ATC) Level 4 term and preferred drug name. Medication summaries will be sorted alphabetically by ATC Level 4 and by preferred drug name within ATC Level 4 for the ITT and Safety Analysis Sets. Subjects will be counted only once for each medication class and each preferred drug name.

Concomitant medications used during the Pegloticase + MTX Period will be summarized by "as-assigned" infusion duration group for the safety analysis set.

Concomitant medications will be coded using the World Health Organization Drug (WHO Drug) Global B3 March 2020 dictionary.

Prior medications, concomitant medications, and medications during the Follow-up Period will be listed together with a designation to identify the period(s) of usage and sorted by start date. The listing will also include the infusion duration that corresponds to the start of the concomitant medication (as described in Treatment Windowing for "As-Treated" Summaries (Section 3.1.6)). For determination of period(s) of use, missing date imputation rules are provided in Medication Dates (Section 3.2.1).

For medications with completely missing dates, the following rules will be used to assign prior, concomitant, and follow-up (concomitant medications used > 30 days after the last dose of Pegloticase or MTX in the Pegloticase + MTX Period):

Medication Start Date	**Medication End Date**	**Prior**	**Concomitant in MTX Run-in Period**	**Concomitant in Pegloticase + MTX Period**	**Follow-up (> 30 days after last dose of Pegloticase or MTX in the Pegloticase + MTX Period)**
Unknown	Unknown	Yes	Yes	Yes	Yes
Unknown	< first dose of MTX	Yes	No	No	No
Unknown	≥ first dose of MTX and < first dose of Pegloticase	Yes	Yes	No	No
Unknown	≥ first dose of Pegloticase and ≤ 30 days after last	Yes	Yes	Yes	No

Medication Start Date	Medication End Date	Prior	Concomitant in MTX Run-in Period	Concomitant in Pegloticase + MTX Period	Follow-up (> 30 days after last dose of Pegloticase or MTX in the Pegloticase + MTX Period)
	Pegloticase/MTX dose				
Unknown	≥ first dose of Pegloticase and > 30 days after last Pegloticase/MTX dose	Yes	Yes	Yes	Yes
< first dose of MTX	Unknown	Yes	Yes	Yes	Yes
≥ first dose of MTX and < first dose of pegloticase	Unknown	No	Yes	Yes	Yes
≥ first dose of pegloticase and ≤ 30 days after last pegloticase/MTX dose	Unknown	No	No	Yes	Yes
> 30 days after last pegloticase/MTX dose	Unknown	No	No	No	Yes

Any medication with a start date prior to the date of first dose of treatment in the MTX Run-in Period will be considered a prior medication.

The following medications will be considered concomitant in the MTX Run-in Period:

- A medication with a start date on or after the first dose date of MTX in the MTX Run-in Period but excluding medications with:
    - Start date on or after the first infusion date of pegloticase and
    - Start date more than 30 days after the last MTX dose, for subjects who did not receive an infusion of pegloticase.
- Medications with a partial start date with month and year of start provided and the year of start and month of start match the month and year of first MTX date and match the month and year of first pegloticase infusion will be classified as being used in the MTX Run-in Period and in the Pegloticase + MTX Period.
- A medication with a start date prior to the first dose date of MTX in the MTX Run-in Period with a stop date strictly after the first dose date of MTX in the MTX Run-in Period

- A medication with a start date prior to the first dose date of MTX in the MTX Run-in Period that was ongoing.

The following medications will be considered concomitant in the Pegloticase + MTX Period:

- A medication with a start date on or after the first infusion date of pegloticase but excluding medications with start date more than 30 days after the date of the end of the last pegloticase or MTX infusion.
- A medication with a start date prior to the first infusion date of pegloticase in the Pegloticase + MTX Period with a stop date strictly after the first infusion date of pegloticase in the Pegloticase + MTX Period.
- A medication with a start date prior to the first infusion date of pegloticase in the Pegloticase + MTX Period that was ongoing.
- Medications with a partial start date with month and year of start provided and the year of start and month of start match the month and year of first MTX date and match the month and year of first pegloticase infusion will be classified as being used in the MTX Run-in Period and in the Pegloticase + MTX Period.

The following medications will be considered in the Follow-up Period:

- Any medications with 1) a start date prior to 30 days after last dose of study medication (MTX or pegloticase) that continued use or had a stop date on or after 30 days after the last dose of study medication, or 2) a medication with a start date more than 30 days after the last dose of study medication

Concomitant procedures will be listed.

3.4 Endpoint Analysis

Potential intercurrent events (ICE) like discontinuing from the treatment may occur during the study. Subjects who discontinue from the treatment will be encouraged to stay in the study after and data will be collected through planned study completion. These intercurrent events will be addressed using different strategies in the efficacy and safety analyses as appropriate.

In general, treatment policy strategy will be used to account for the ICEs for defining estimands corresponding to continuous efficacy endpoints. For binary responder endpoints, composite strategy will be used. Safety endpoints will be assessed using a while-on-treatment strategy.

3.4.1 Primary Endpoint Analysis

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

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

Population	Safety Analysis Set for the cohort chosen to be most desirable for infusion
Endpoint	Incidence of subjects experiencing IRs (including anaphylaxis) related to pegloticase
ICE	Early discontinuation of pegloticase
ICE Strategy	Only events that occur while the subject is receiving study pegloticase will be counted
Population-level Summary	Proportion of subjects who experience an IR (including anaphylaxis) related to pegloticase between Day 1 and Week 24

The primary analysis of the primary endpoint will be based on events adjudicated as IR (including anaphylaxis) by the adjudication committee. Adverse events adjudicated as IR will be considered to be related to pegloticase, regardless of the investigator causality assessment. The count and proportion of subjects with an IR (including anaphylaxis) related to pegloticase will be summarized, along with an a two-sided 95% exact (Clopper-Pearson) confidence interval for the proportion. The primary endpoint will be met if the upper bound of the 95% confidence interval is < 13%. Additionally, this endpoint will be analyzed for each of the other infusion duration cohorts. An additional summary based on reported events will be provided.

3.4.2 Secondary Endpoint Analyses

3.4.2.1 Month 6 Responders

The estimand for the secondary endpoint for Month 6 responders is defined by the following:

Population	Modified Intent-to-Treat Analysis Set for the cohort chosen to be most desirable for infusion
Endpoint	Proportion of responders during Month 6
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, or have < 2 sUA from separate visits available 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	Proportion of subjects who meet the response definition during Month 6

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

The number and proportion of subjects meeting the Individual Subject sUA Discontinuation Criteria will be summarized descriptively as part of the secondary endpoints.

A subject will be declared a non-responder if the subject had sUA level > 6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit. In addition, a subject who withdraws from the study for any reason (other than meeting Individual Subject sUA Discontinuation Criteria) after the first dose of pegloticase in the pegloticase + MTX Period and prior to or during Month 6 will be considered a Month 6 non-responder if sUA values are not collected at the planned timepoints. The proportion of Month 6 responders by pegloticase baseline and post baseline ADA (positive /negative) status will be summarized similarly as the above. Please see Section 3.6.3.4 for the definition of pegloticase baseline and post baseline ADA status.

The proportion of time that the sUA level is below 6 mg/dL during Month 6 is defined as the ratio of the time during which the sUA level remains below 6 mg/dL (using linear interpolation, if necessary) to the entire time interval during Month 6. Results from visits where an infusion was not performed (e.g. subject discontinued pegloticase but remained in study) will be used when available. The subject-specific proportion of time during the period during which the sUA was less than 6 mg/dL will be summarized using descriptive statistics. If a subject has ≤ 1 data point in the period, then the proportion of time will not be calculated.

The number and proportion of subjects that discontinued treatment due to the stopping rule will be summarized. In addition, the number and proportion of subjects missing all data in analysis period will be summarized.

3.4.2.2 IR Leading to Discontinuation of Treatment, Anaphylaxis, or Meeting Individual Subject sUA Discontinuation Criteria

The estimand for the secondary endpoints related to IRs leading to discontinuation and meeting sUA discontinuation criteria is defined by the following:

Population	Safety Analysis Set for the cohort chosen to be most desirable for infusion
Endpoint	Incidence of subjects experiencing IR leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA Discontinuation Criteria (two consecutive pre-infusion sUAs > 6 mg/dL Time to any of the following events: IR leading to discontinuation of treatment, anaphylaxis, or meeting Individual Subject sUA

	Discontinuation Criteria (two consecutive pre-infusion sUAs > 6 mg/dL
ICE	Early discontinuation of pegloticase
ICE Strategy	Only events that occur while the subject is receiving study pegloticase will be counted
Population-level Summary	Proportion of subjects who experience an IR (including anaphylaxis) related to pegloticase between Day 1 and Week 24 Median time to the first event

The proportion of subjects experiencing any of the following events (composite endpoint and for each individual component) will be summarized descriptively along with a two-sided 95% exact (Clopper-Pearson) confidence interval:

The time to subjects experiencing any of the following events:

- IR leading to discontinuation of treatment
- Anaphylaxis or
- Meeting Individual Subject sUA Discontinuation Criteria

will be summarized descriptively for the safety analysis set as a composite endpoint by assigned infusion duration group. Kaplan Meier (KM) estimates of the time to event from Day 1 will be reported along with the corresponding quartiles and a 95% CI for the median time if there are sufficient number of events to perform the analysis. An estimate of the cumulative incidence rate by Week 24 will also be calculated. For the analysis of the composite endpoint, subjects who do not experience any of the aforementioned events will be censored at the time of last infusion.

Time to event to each individual component of the composite endpoint will also be summarized descriptively. To account for the competing events nature of these events, the cumulative incidence function will be determined and estimates of the cumulative incidence by Week 24 and median time to event for each event will be summarized with a 95% CI for the median time (if available). Subjects who do not experience any of the competing events or the event of interest will be censored at the date of their last infusion.

A competing event is defined as any of the components of the composite endpoint or discontinuation from treatment for any reason. Other competing events may be included in the analysis, as needed.

The time to an event will be calculated by date of event – date of first dose of treatment + 1. Patients who do not experience an event will be censored at time given by date of last dose of treatment - date of the first dose of the treatment + 1.

Events of anaphylaxis and IRs are collected as “reported events” and “adjudicated events”. For all relevant endpoints, separate analyses will be created for reported events and adjudicated events.

3.4.3 Exploratory Endpoint Analyses

[redacted]

3.5 Analysis of Pegloticase Pharmacokinetics, Methotrexate Polyglutamates, and Anti-Drug Antibodies

3.5.1 Pegloticase and MTX PK

Serum samples for pegloticase PK analysis will be collected approximately 15 minutes to 2 hours after the end of infusion on Day 1; prior to infusion and approximately 15 minutes to 2 hours after the end of the infusion at Weeks 2, 6, 12 and 20. An additional PK sample will be collected at the End-of-Study (Week 24)/Early Termination Visit.

PK summaries will be done for the PK analysis set. MTX polyglutamate summaries will be done for the mITT analysis set. All results will be presented by 'as assigned' infusion duration group.

The following presentations of subject serum pegloticase concentration data covered in this SAP will be provided for pegloticase:

- A listing including subject, week/time point (actual, planned), treatment and serum concentrations. End of infusion sampling times are expressed relative to the start time of infusion.

- A table summary of serum pegloticase concentrations at each time point (n; mean, SD, coefficient of variation (CV)% calculated as 100% × SD/mean, minimum, 25th percentile, median, 75th percentile, maximum, geometric mean and geometric CV%) will be provided for the PK analysis set. Similar tables will be produced by Month 6 sUA responder status.

Further, the mean and CV% of pegloticase concentrations will be provided by visit in the subset of subjects who are ADA positive (defined as positive for anti-PEG or anti-uricase antibodies at any visit) and ADA negative (defined as negative for both anti-PEG and anti-uricase antibodies at all visits) for each visit.

All concentrations BLQ after the first pegloticase infusion will be imputed by half of LLOQ for the analysis summaries. The number of BLQ records will be summarized. Concentrations more than 17 days after the last infusion will be excluded from the summary.

Concentrations of MTX polyglutamate are measured for 5 active metabolites (MTX-PG1, MTX-PG2, MTX-PG3, MTX-PG4, MTX-PG5). The summary of individual 5 MTX polyglutamate values, PG1-2 (i.e., PG1 + PG2), PG3-5 (i.e., PG3 + PG4 + PG5), PG4-5 (i.e., PG4 + PG5), and total PG1-5 (i.e., PG1 + PG2 + PG3 + PG4 +PG5) over time for all mITT subjects, as well as by Month 6 sUA responders and Month 6 sUA non-responders will be provided. All concentrations BLQ are excluded from the analysis summaries. When calculating the sum over MTX-PGs, values of '<5' count as 0 in the sum.

A plot of the mean total PG1-5, and individual 5 MTX polyglutamate mean values over time will be provided for the mITT set by Month 6 sUA response status (responder vs. non-responder) for each infusion duration group.

A listing of MTX polyglutamate concentrations will be provided, showing the subject, treatment, visit, collection date and time, study day relative to first MTX treatment date, and the 5 MTX polyglutamate values along with total MTX polyglutamate values (PG1-5).

3.5.2 Anti-Drug Antibodies

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

For anti-PEG IgG antibodies, using the safety analysis set, the number and percentage of subjects who meet the following criteria will be summarized by scheduled timepoint and overall:

- ADA positive at pegloticase baseline
- ADA negative at pegloticase baseline
- ADA negative at pegloticase baseline and ADA positive at post-pegloticase baseline
    - ADA positive at pegloticase baseline with increase in titer from pegloticase baseline
    - ADA negative at pegloticase baseline and ADA positive at post-pegloticase baseline or with increase in titer from pegloticase baseline (i.e. ADA positive status post-baseline)

For anti-uricase IgG antibodies, the number and percentage of subjects with ADA positive at pegloticase baseline and post-pegloticase baseline will be summarized by scheduled timepoint.

Kaplan-Meier estimates of the time to positive anti-PEG response (for subjects who were negative at baseline) or increase in anti-PEG titer (for subjects who were positive at baseline), and the time to anti-uricase response with 25th percentile, median, 75th percentile, and 95% CI, along with a Kaplan-Meier curve will be produced. Subjects who never have a positive anti-PEG response or increase in titer will be censored at the date of their last visit (3 month follow up visit, or, if the subject did not attend this visit, then whatever last visit they have on record). Antibody result from both scheduled and unscheduled visits will be included for the time to event analysis.

Anti-PEG and anti-uricase titer will be summarized descriptively with mean and CV% by study visit. Additionally, Anti-PEG titers at the last pegloticase infusion and post-treatment will be summarized for ADA positive post-baseline subjects.

All results will be presented by ‘as assigned’ infusion duration group.

3.6 Safety Analysis

3.6.1 General Conventions

Unless otherwise specified, safety analyses will be based on the safety analysis set and the ITT analysis set, depending on the treatment period. The ITT analysis set will be used for analysis of safety data during the MTX Run-in Period prior to Day 1 and the safety analysis set will be used for analysis in the Pegloticase + MTX Period or summaries across both treatment periods. Summaries will be presented by “as-assigned” infusion duration group. Analyses done by “as-treated” group may be done, if warranted.

Refer to Section 3.1.6 for additional details regarding infusion duration group for reporting.

3.6.2 Extent of Exposure

Study drug exposure will be summarized by 'as assigned' infusion duration group for the following statistics: duration of treatment (in days), number of infusions (pegloticase only), and total dose received for MTX and pegloticase.

The usage of prophylaxis treatments (folic acid, IR usage of fexofenadine the day prior to pegloticase infusion, IR prophylaxis of fexofenadine and acetaminophen the morning prior to infusion, and IR prophylaxis of methylprednisolone immediately prior to infusion) will be provided in listings only. Reasons for infusion interruptions will be provided in the listings.

For the MTX Run-in Period, the following will be summarized using the ITT analysis set:

- Days in MTX Run-in Period
- Duration of treatment, defined as the Day 1 visit date – first dose date of MTX for subjects in the mITT analysis set and last dose of MTX – first dose of MTX + 1 for subjects who do not continue into the Pegloticase + MTX Treatment Period (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)
- Total MTX dose taken between the first and last dose dates in the MTX Run-in Period, inclusive (in mg) (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)
- Average weekly MTX dose (in mg) (total dosage for the MTX Run-in Period divided by number of doses taken during the MTX Run-in Period divided by [days in MTX Run-in Period / 7]) (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)
- Number of subjects with MTX dosage reductions from planned 15 mg/week.

For the Pegloticase + MTX Period, the following will be summarized for the safety analysis set:

- Pegloticase
    - Days in Pegloticase + MTX Period
    - Duration of Pegloticase exposure in days defined as the last Pegloticase date – first Pegloticase dosing date + 1 (summarized with descriptive statistics of mean, SD, median, minimum and maximum)
    - Number of pegloticase infusions received (summarized with frequency summary and also with descriptive statistics of mean, SD, median, minimum, and maximum)
    - Duration of Pegloticase infusion in minutes
    - At least one planned infusion duration changed from assigned infusion duration
    - Proportion of subjects planned duration different from assigned infusion duration

  - At each scheduled Pegloticase infusion visit the following will be summarized:
    - Number of subjects receiving a complete infusion (i.e. full dose administered)
    - Number of infusions administered without interruption
    - Number of subjects with an interrupted infusion

- MTX
  - Days in Pegloticase + MTX Period
  - Duration of MTX treatment during the Pegloticase + MTX Period, defined as the last MTX date – Day 1 visit date + 1, for dates occurring within the Pegloticase + MTX period
  - Total MTX dose (in mg) received during the Pegloticase + MTX period
  - Average weekly MTX dose (in mg) (total dose for the Pegloticase + MTX Period divided by number that patient's doses taken during the Pegloticase + MTX Period divided by [days in Pegloticase + MTX Period / 7])) (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)
  - Number of subjects with MTX dosage reductions from planned 15 mg/week.

For the overall study, the following will be summarized using the safety analysis set:

- MTX
  - Days in study
  - Duration of MTX treatment, defined as the last MTX date – first MTX dosing date + 1
  - Cumulative MTX dose (in mg) received
  - Number of subjects with MTX dosage reductions from planned 15 mg/week.
  - Average weekly MTX dose (in mg) (average of each subject's total dose for the Pegloticase + MTX Period divided by number that patient's doses taken during the Pegloticase + MTX Period divided by [days in Pegloticase + MTX Period / 7])) (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)

Subjects who had a dose adjustment/interruption of MTX due to tolerability issues will be listed.

3.6.3 Adverse Events

3.6.3.1 Definitions by Period

AEs will be classified as pre-treatment, treatment-emergent AEs (TEAEs) during the MTX Run-In Period, TEAEs during the Pegloticase + MTX period, or Follow-up AEs. The AE's will be classified as follows:

- Pre-treatment: Onset date prior to the first dose of MTX.
- TEAE during the MTX Run-in Period: Onset date on or after the first dose of MTX until the first pegloticase infusion.
- For subjects who do not receive pegloticase, also include AEs with onset date within 30 days after the last dose of MTX.
- TEAE during the Pegloticase + MTX Period: Onset date on or after the start of the first pegloticase infusion through 30 days after the last dose of pegloticase and/or MTX (whichever is later).
- Follow-up AE: Onset date >30 days after last dose of pegloticase and/or MTX (whichever is later).

3.6.3.2 Overall Summaries

An overall summary of TEAEs for the ITT analysis set will be provided for the MTX Run-in Period, including the number and percentage of subjects with each AE type as well as the number of events for each of the following:

- TEAEs
- Serious TEAEs
- TEAEs related to MTX
- Serious TEAEs related to MTX
- TEAEs with a Rheumatology Common Toxicity Criteria (CTC) of 3 or higher
- TEAEs leading to permanent withdrawal of MTX
- TEAEs related to MTX leading to permanent withdrawal of MTX
- TEAEs leading to death

An overall summary of TEAEs for the safety analysis set will be provided for the Pegloticase + MTX Period, including the number and percentage of subjects with each AE type as well as the number of events for each of the following:

- TEAEs

- Serious TEAEs
- TEAEs related to pegloticase
- TEAEs related to MTX
- Serious TEAEs related to pegloticase
- Serious TEAEs related to MTX
- TEAEs with a Rheumatology CTC of 3 or higher
- TEAEs leading to permanent withdrawal of pegloticase
- TEAEs related to pegloticase leading to permanent withdrawal of pegloticase
- TEAEs leading to permanent withdrawal of MTX
- TEAEs related to methotrexate leading to permanent withdrawal of MTX
- TEAEs leading to death
- TEAEs of special interest

An overall summary of Follow-up AEs for the safety analysis set will be provided, including the number and percentage of subjects with each AE type as well as the number of events for each of the following.

- AEs
- Serious AEs
- AEs with a Rheumatology CTC of 3 or higher
- AEs leading to death

Percentages for the overall summary of AEs during follow-up will be based on the number of subjects in the safety analysis set who had follow-up more than 30 days after last dose of medication.

3.6.3.3 Additional Summaries

Additional summaries displaying the number and percentage of subjects experiencing AE's overall and by System Organ Class (SOC) and Preferred Term (PT) will be provided for time periods as shown in the following table. Note that for pre-treatment AE's no summaries will be provided, but these events will be listed.

Additional summaries displaying the number and percentage of subjects experiencing AE's

Summary Overall and by SOC and PT	**MTX Run-in Period**	**Pegloticase + MTX Period**	**Follow-up Period**
TEAEs	X, Y*	Y*	Y
Serious adverse events (SAEs)	X, Y*	Y*	Y
TEAEs by maximum severity	X, Y	Y	Y
TEAEs related to MTX	X, Y*	Y*	Y
TEAEs related to pegloticase		Y*	Y
TEAEs leading to permanent withdrawal of MTX	X, Y*	Y*	
TEAEs leading to permanent withdrawal of pegloticase		Y*	
TEAEs related to MTX by maximum severity	X, Y	Y	Y
TEAEs related to Pegloticase by maximum severity		Y	Y
SAEs leading to permanent withdrawal of MTX	X, Y*	Y*	
SAEs leading to permanent withdrawal of pegloticase		Y*	
TEAEs of COVID-19 by maximum severity	X, Y	Y	Y

* = summary includes exposure-adjusted incidence rate (EAIR)
X = ITT set; Y = safety analysis set;
overall and by System Organ Class (SOC) and Preferred Term (PT) will be provided for time periods as shown in the following table. Note that for pre-treatment AE's no summaries will be provided, but these events will be listed.

The exposure-adjusted incidence rate (EAIR) will be calculated based on MTX exposure and pegloticase exposure, and will be provided for the summaries as noted in the table above, as well as the overall summary of TEAEs during the Run-in Period and the Pegloticase + MTX Period. For summaries during the Pegloticase + MTX period, the EAIR will be presented for both MTX and pegloticase exposures.

The EAIR is calculated as the total number of subjects with the event divided by the person-years (PY) of exposure for the event. The following formulas will used for the calculation of PY for each event and treatment in each period:

Run-in Period

- For subjects with the event, MTX PY = date of first occurrence of the event – date of first dose of MTX in the Run-in Period + 1.

- For subjects without the event, MTX PY = date of last MTX dose – date of first MTX dose +1 for subjects who do not enter the Pegloticase + MTX Period and PY = Day 1 visit date – date of first dose of MTX in the Run-in Period for subjects who do enter the Pegloticase + MTX Period.

Pegloticase + MTX Period

- For subjects with the event, PY (for both MTX and pegloticase exposure) = date of first occurrence of the event – Day 1 visit date + 1.

- For subjects without the event, PY = date of last dose of MTX (for MTX PY) or pegloticase (for pegloticase PY) – Day 1 visit date + 1

The PY will be summed over all subjects exposed to study drug and divided by 365.25 to get the total PY of exposure for each event.

For summaries by SOC, PT, and maximum severity, a subject will only be counted once within an infusion duration group for each SOC based on the maximum intensity level reported for that SOC and once for each unique PT within that SOC level at the maximum intensity level reported for that PT. Similar logic will be applied for summaries by SOC, PT, and relatedness.

For summaries by SOC and PT only, a subject will be counted at most once within an infusion duration group at the SOC level and at most once at each unique PT within the SOC level. Summaries presenting the frequency of TEAEs by SOC and PT will be ordered alphabetically by SOC and then, within a SOC, alphabetically by PT.

All AEs will be listed. The listing of all AEs will also include the infusion duration that corresponds to the start date of the adverse event (as described in Treatment Windowing for "As-Treated" Summaries (Section 3.1.6). TEAEs and the period of onset will be identified in each listing. In total, the following sets of AEs will be provided as listings:

- Adverse Events
- AEs leading to withdrawal of MTX
- AEs leading to withdrawal of pegloticase
- AEs with CTC grade of 3 or higher
- AEs of special interest: major adverse cardiovascular events (reported and adjudicated)
- AEs of special interest: symptoms related to infusion reaction or anaphylactic reactions (reported and adjudicated)
- AEs of special interest: gout flares
- AEs occurring >30 days after last pegloticase infusion
- Serious AEs
- AEs for subjects who died

- AEs for subjects with suspected or confirmed COVID-19

Severity of AE's will be determined using the Rheumatology Common Toxicity Criteria v2.0.

3.6.3.4 AEs of Special Interest

Incidence of IRs, anaphylaxis, gout flares and Major Adverse Cardiovascular Events (MACE) will be summarized for the safety analysis set by infusion duration group. Separate summaries will be produced for adjudicated events and reported events (only applies to IRs, anaphylaxis and MACE events – gout flares are not adjudicated).

Summaries of IRs and anaphylaxis will group events by 3 categories:

- Anaphylaxis
- Infusion reactions including anaphylaxis
- Infusion reactions excluding anaphylaxis

Both the investigator-reported and adjudicated events and the associated signs and symptoms will be summarized separately by severity, and the time relative to the most recent pegloticase infusion for each category above. Signs and symptoms will also be summarized by SOC and PT.

Time relative to the most recent pegloticase infusion will be categorized as: during infusion, ≤ 2 hours after infusion, > 2 hours to 24 hours after infusion, and > 24 hours after infusion. If the time of the infusion reaction or anaphylaxis is missing, the category will be assigned as "Missing".

Serious events and the associated symptoms will be summarized by SOC and PT for each category.

The number of events per subject per treatment infusion duration group, the number of events and serious events per infusion, and the number of subjects with the first event by infusion number will be summarized as well for each category. IRs (including anaphylaxis) that occur on the same date will be considered one event.

In addition, the number and percentage of subjects with adjudicated IRs, including anaphylaxis, will summarized by severity of event using the following categories for both anti-PEG and anti-uricase antibodies:

- ADA status at baseline (positive or negative)
- ADA status post-baseline (positive or negative)
    - ADA positive post-baseline: negative at baseline and positive at any post-baseline time point, or positive at baseline and with an increase in titer at post-baseline timepoint
    - ADA negative post-baseline: defined as negative at all time points, or positive at baseline and without post-baseline increases in titer from baseline titer

MACEs are defined as: including non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure. The following search algorithm will be used to identify possible MACEs:

- For cardiovascular death: any fatal cases with following terms
    - Standardized MedDRA Queries (SMQ): Myocardial infarction (broad), Ischaemic Central Nervous System (CNS) Vascular conditions (narrow); Haemorrhagic central nervous system vascular conditions (narrow), Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (narrow), Embolic and thrombotic events (arterial, venous, vessel type unspecified and mixed arterial and venous) (narrow), Cardiac failure (broad), shock-associated conditions (narrow), Torsade de pointes/QT prolongation (narrow), Arrhythmia related investigations, signs and symptoms (broad), Cardiomyopathy (broad), Supraventricular tachyarrhythmias (narrow), Ventricular tachyarrhythmias (narrow), Conduction defects (narrow)
    - All PTs under SOC of Cardiac disorders
    - HLGT Aneurysm
- For non-fatal myocardial infarction: SMQ Myocardial infarction (broad)
- For non-fatal stroke: SMQ: Ischaemic Central Nervous System (CNS) Vascular conditions (narrow); Haemorrhagic central nervous system vascular conditions (narrow); Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (narrow)
- Congestive heart failure: SMQ Cardiac failure (broad)

The cardiovascular events identified using the aforementioned criteria and the adjudicated cardiovascular events will be summarized by SOC and PT for the MTX Run-in Period and Pegloticase + MTX Period for the safety analysis set. EAIR of pegloticase and MTX will be summarized for the Pegloticase + MTX Period.

The number and percentage of subjects who experienced a gout flare (recorded in the AE eCRF), and number of gout flares per subject will be summarized for the MTX Run-in Period using the ITT analysis set. Percentages will be based on the number of subjects in the ITT analysis set.

The number and percentage of subjects who experienced a gout flare and number of gout flares per subject during the MTX Run-in Period and the Pegloticase + MTX Period (recorded in the AE eCRF) will be provided for the safety analysis set.

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

3.6.3.5 Additional Safety Endpoints

The following safety endpoints will be summarized descriptively for the safety analysis set by assigned infusion duration:

- The proportion of subjects who experienced IR leading to slowing down of the infusion rate or discontinuation of treatment (composite endpoint and for each individual component; separate analyses for reported events and adjudicated events) (safety analysis set).

- The proportion of subjects who completed all infusions over the assigned treatment duration length or a lesser time, without clinically requiring an increased infusion time (safety analysis set) will be summarized. Subjects who discontinue treatment prematurely will not be considered to have completed all infusions.

- The proportion of infusions completed over the assigned duration length or a lesser time, without clinically requiring an increased infusion time will be summarized for the safety analysis set on the infusion level and on the subject-specific level using two different denominators each:

    - Infusion level (will be reported as a proportion and a percentage):

        - The number of infusions completed over the assigned treatment duration length or a lesser time, without clinically requiring an increased infusion time / total number of infusions planned for all subjects (12 x number of subjects in the assigned treatment duration group).

        - The number of infusions completed over the assigned treatment duration length or a lesser time, without clinically requiring an increased infusion time / total number of infusions completed prior to discontinuation of treatment planned for all subjects.

    - Within-subject level (reported descriptively as a continuous variable with 95% sign test-based confidence intervals provided around the median):

        - For each subject, the subject-specific number of infusions completed over the assigned treatment duration length or a lesser time, without clinically requiring an increased infusion time / subject's total number of infusions planned (12 total).

        - For each subject, the subject-specific number of infusions completed over the assigned treatment duration length or a lesser time, without clinically requiring an increased infusion time / subject's total number of completed infusions prior to discontinuation of treatment**.**

- The time to subjects' first IR and first instance of IR leading to discontinuation of treatment or slowing down of the infusion rate will be analyzed. KM estimates of the time to event from Day 1 will be reported along with the corresponding quartiles and a 95% CI for the median time (if available). The event "first instance of IR leading to discontinuation of treatment or slowing down of the infusion rate" will be analyzed both as a composite endpoint and individually.

3.6.4 Laboratory Tests

Laboratory test results, including urine albumin: creatinine ratio, will be summarized by treatment period, infusion duration group, and study visit. For summaries of visits during the

Pegloticase + MTX Period, only data collected within 30 days (inclusive) after the last dose of MTX or pegloticase will be included. Results from the 3 Month Follow-up visit will also be summarized.

Shift-from-MTX baseline tables for laboratory parameters by Common Terminology Criteria for Adverse Events (CTCAE) grade will be presented. For tests where the CTCAE criteria are available, grade will be assigned programmatically, and shift tables will be based on the derived CTCAE grade. The CTCAE version 4.03 will be used for these summaries. Laboratory test results without established CTCAE grading criteria will also be classified relative to the normal reference range (normal, low, or high) and summarized as shift tables.

Laboratory summaries will be provided for both safety (both treatment periods) and ITT analysis sets (MTX Run-in Period only). Shift tables and change from baseline will be reported using the following baseline visits and periods:

- MTX Run-in Period: summarized for ITT analysis set using MTX baseline
- MTX Run-in Period and Pegloticase + MTX Period: summarized for safety analysis set using MTX baseline
- Pegloticase + MTX Period: summarized for safety analysis set using pegloticase baseline

A summary of elevated liver function test values, Hy's law, and subjects meeting MTX intolerance criteria (hematology only) will be provided for the safety analysis set by visit and overall for the MTX Run-in Period and the Pegloticase + MTX Period. Analyses of liver function tests and MTX intolerance criteria (hematology only) will also be done for the ITT for only the MTX Run-in period.

- alanine aminotransferase > ULN, 2xULN, 3xULN, 5xULN, 10xULN, and 20xULN
- aspartate aminotransferase > ULN, 2xULN, 3xULN, 5xULN, 10xULN, and 20xULN
- alkaline phosphatase ≥ 1.5xULN, 2.5xULN, and 3xULN
- total bilirubin ≥ 1.5xULN, 2xULN, and 3xULN

Hy's law:

- (alanine aminotransferase or aspartate aminotransferase > 3xULN) and total bilirubin ≥ 2xULN on the same date
- (alanine aminotransferase or aspartate aminotransferase > 3xULN) and total bilirubin ≥ 2xULN and alkaline phosphatase < 2xULN on the same date

MTX intolerance criteria (hematology):

- WBC < 3.5 x 10^9/L
- Platelets < 75 x 10^9/L
- Hematocrit < 32%

Subjects who meet either the liver function tests, Hy's law or MTX intolerance criteria will be listed, with the corresponding lab results.

A summary of albumin: creatinine ratio by visit will be provided for the Pegloticase + MTX Period using the Safety analysis set.

Line plots for select laboratory values over time (including chemistry, hematology, and albumin: creatinine ratio) may be provided.

3.6.5 Other Safety Analyses

Vital signs, including BP, respiratory rate, temperature and heart rate, will be summarized by "as assigned" infusion duration group, study visit and change from baseline.

Vital signs summaries will be provided for both Safety (both treatment periods and Pegloticase + MTX Period only) and ITT (MTX Run-in Period only) analysis sets. Vital sign measurements that are monitored as a result of an infusion-associated event will not be included in the descriptive summaries but will be presented in subject listings. See Definition of Baseline (Section 3.1.3) for more information.

ECG results for the ITT analysis set at screening will be summarized by the number of normal, abnormal non-clinically significant, and abnormal clinically significant results. A summary of subjects in the safety analysis set with ECGs collected in the Pegloticase + MTX Period will be provided that includes the number of any abnormal clinically significant results.

For the summary tables, only data collected within 30 days (inclusive) after the last dose of MTX or pegloticase will be included for visits during the Pegloticase + MTX Period.

Physical exam results will be provided in the subject listings.

3.7 Other Analyses

3.7.1 C-Reactive Protein

C-Reactive protein will be summarized by infusion duration group for the safety analysis set during the Pegloticase + MTX Period. The summary will include the change from pegloticase baseline. End of pegloticase and end of study results will be given their own timepoint with no visit windowing.

3.8 Interim Analysis

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

- After 3 subjects complete at least 3 infusions at one assigned infusion duration level.
- After 6 subjects complete at least 3 infusions at one assigned infusion duration level.

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

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

Efficacy and safety data may be summarized after all subjects have completed the Pegloticase + MTX Treatment Period. Final analysis of all data will occur when all subjects have discontinued or completed the study (including Follow-up visits).

No type I error adjustment will be made with respect to these interim analyses.

4 Analysis Change from the Protocol

Exploratory endpoints [redacted]

5 Reference List

FitzGerald, J.D., et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Rheumatol, 2020;72: 879-895. https://doi.org/10.1002/art.41247

DocuSign

Certificate Of Completion

Envelope Id: 4CCC6E01B93041A7A13EBD8CA2E41EED
Status: Completed
Subject: Complete with DocuSign: HZNP-KRY-403 SAP v2.0 Final.docx
Source Envelope:
Document Pages: 47
Signatures: 3
Envelope Originator:
Certificate Pages: 5
Initials: 0
[redacted]
AutoNav: Enabled
1 Horizon Way
EnvelopeId Stamping: Disabled
Deerfield, 60015
Time Zone: (UTC-06:00) Central Time (US & Canada)
[redacted]
IP Address: 198.178.220.7

Record Tracking

Status: Original
1/19/2024 4:05:56 PM
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: A1B826E5-414D-483F-8E08-CB3A12F33DB4 Using IP Address: 198.178.220.7 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 1/19/2024 4:11:38 PM Viewed: 1/19/2024 5:29:21 PM Signed: 1/19/2024 5:30:08 PM
Electronic Record and Signature Disclosure: Accepted: 1/19/2024 5:29:21 PM ID: ff7c48a8-311e-4904-bb52-6d2e6facf49c		
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 22025659-5FE9-4748-938D-9D7EA8DA426E Using IP Address: 198.178.220.7 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/19/2024 4:11:37 PM Viewed: 1/19/2024 4:15:38 PM Signed: 1/19/2024 4:17:16 PM
Electronic Record and Signature Disclosure: Accepted: 1/2/2024 9:18:53 AM ID: 9863c73a-6355-4b6b-877c-006ddcc20364		

Signer Events	Signature	Timestamp
[redacted]	[redacted]	Sent: 1/19/2024 4:11:37 PM Viewed: 1/22/2024 12:13:09 AM Signed: 1/22/2024 12:13:53 AM
Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: 9B097010-E26D-4586-A9BD-98BA31B78658 Using IP Address: 76.169.225.73 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	
Electronic Record and Signature Disclosure: Accepted: 12/1/2023 2:57:48 PM ID: ce7b9f75-c9f1-47ca-b858-956abc349f36		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	1/19/2024 4:11:38 PM
Certified Delivered	Security Checked	1/22/2024 12:13:09 AM
Signing Complete	Security Checked	1/22/2024 12:13:53 AM
Completed	Security Checked	1/22/2024 12:13:53 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Record and Signature Disclosure created on: 11/8/2016 12:15:45 PM
Parties agreed to: [redacted]

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Horizon Pharma, Inc. - Part 11 (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through your DocuSign, Inc. (DocuSign) Express user account. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to these terms and conditions, please confirm your agreement by clicking the 'I agree' button at the bottom of this document.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. For such copies, as long as you are an authorized user of the DocuSign system you will have the ability to download and print any documents we send to you through your DocuSign user account for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. To indicate to us that you are changing your mind, you must withdraw your consent using the DocuSign 'Withdraw Consent' form on the signing page of your DocuSign account. This will indicate to us that you have withdrawn your consent to receive required notices and disclosures electronically from us and you will no longer be able to use your DocuSign Express user account to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through your DocuSign user account all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Horizon Pharma, Inc. - Part 11:
You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: [redacted]

To advise Horizon Pharma, Inc. - Part 11 of your new e-mail address
To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to us at [redacted] and in the body of such request you must state: your previous e-mail address, your new e-mail address. We do not require any other information from you to change your email address..
In addition, you must notify DocuSign, Inc to arrange for your new email address to be reflected in your DocuSign account by following the process for changing e-mail in DocuSign.

To request paper copies from Horizon Pharma, Inc. - Part 11
To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an e-mail to [redacted] and in the body of such request you must state your e-mail address, full name, US Postal address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Horizon Pharma, Inc. - Part 11
To inform us that you no longer want to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your DocuSign account, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
ii. send us an e-mail to [redacted] and in the body of such request you must state your e-mail, full name, IS Postal Address, telephone number, and account number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time providing you with the revised hardware and software requirements, at which time you will have the right to withdraw your consent.

Acknowledging your access and consent to receive materials electronically
To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.
By checking the 'I Agree' box, I confirm that:

- I can access and read this Electronic CONSENT TO ELECTRONIC RECEIPT OF ELECTRONIC RECORD AND SIGNATURE DISCLOSURES document; and

- I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and

- Until or unless I notify Horizon Pharma, Inc. - Part 11 as described above, I consent to receive from exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to me by Horizon Pharma, Inc. - Part 11 during the course of my relationship with you.