Study: HZNP-KRY-201

NCT#: 03635957

TITLE:
SAP
Protocol Title: A Multicenter, Efficacy and Safety Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving KRYSTEXXA® (pegloticase) (MIRROR Open-Label [OL])

Date of Document:

SAP: 10 July 2020

Statistical Analysis Plan

Sponsor Name: Horizon Therapeutics Ireland DAC

Protocol Number: HZNP-KRY-201
Protocol Title: A Multicenter, Efficacy and Safety Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving KRYSTEXXA® (pegloticase) (MIRROR Open-Label [OL])

Protocol Version and Date: Version 3.0 Amendment 2 (17Apr2019)

[redacted]

Authors: [redacted]

SAP Version: 2.0

SAP Version Date: 10-Jul-2020

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	12-MAR-2019	[redacted]	Initial Release Version
0.2	10-MAY-2019	[redacted]	2nd Version incorporating protocol Version 3.0 Amendment 2 and comments on initial draft
0.3	06-JUN-2019	[redacted]	3rd version incorporating modifications from 2nd revision.
1.0	19-JUL-2019	[redacted]	Finalization
1.0	22-AUG-2019	[redacted]	Finalization based on comments received
1.0	06-SEP-2019	[redacted]	Finalization based on comments received
1.2	02-Jun-2020	[redacted]	The following are updated based on comments received: 1) Section 6.4, Visit windows are updated for MTX PK and Pegloticase PK; visit date from corresponding CRF page is added 2) Section 7, disposition categories are updated 3) Section 8.3, medications in follow-up period is added; how to determine period of prior or concomitant medications for completely missing dates is added 4) Section 9.1, local lab sUA standardization is removed 5) Section 9.3.4, Pegloticase treatment status is added 6) Section 10, MTX PK summary is updated; ADA summary is updated 7) Section 11.1, MTX dose was corrected to 15 mg/week instead of 15 mg/day; MTX exposure is updated 8) Section 11.3.1, special interest AE is updated for cardiovascular SMQ; gout flare summary by month is added 9) Section 11.4, liver function summary is added 10) Section 15, index of tables is updated to match the table shells 11) Section 16, index of figures is updated to match the figure shells

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
2.0	10-Jul-2020	[redacted]	The following are updated based on comments received: 1) Section 8.3, modified rules to assign medications to study periods; added summary table for medications used for gout treatment 2) Section 9.4.6, subjects with only a single elevated pre-infusion sUA and no subsequent sUA results available is added to the events 3) Section 9.4.8, added 0 will be used for number of joints affected 4) Section 11.3.1, clarified 30 days

I confirm that I have reviewed this document and agree with the content.

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Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
°C	degrees Celsius
°F	degrees Fahrenheit
AE	Adverse event
ATC	Anatomical Therapy Chemical
BID	twice a day
BLQ	Below limits of quantification
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CNS	Central Nervous System
CS	Clinically significant
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DECT	dual-energy computed tomography
dL	deciliter
ECG	Electrocardiogram
eCRF	Electronic CRF
ET	Early termination
GCR	Gout chronic response
GCR20	Gout chronic response – 20% reduction
GCR50	Gout chronic response – 50% reduction
GCR70	Gout chronic response – 70% reduction
GCRn	Gout chronic response – n% reduction
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
HIV	human immunodeficiency virus
IMM	Immunomodulator
ICF	Informed Consent Form
IgG	Immunoglobulin G
IR	Infusion reaction
ITT	Intent-to-Treat

Abbreviation	Description
IV	intravenously
kg	kilogram
KM	Kaplan-Meier
lb	pound
MACE	Major Adverse Cardiovascular Events
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	Minimum
mITT	Modified Intent-to-Treat
mL	milliliter
mmHg	millimeters mercury
MTX	Methotrexate
NCS	Not Clinically significant
NSAID	Non-steroidal anti-inflammatory drug
Oz	Ounces
PK	Pharmacokinetics
PO	orally
PR	Interval from the beginning of the P wave to the beginning of the QRS complex on ECG
PT	Preferred Term
QT	Interval from the beginning of the Q wave and the end of the T wave on ECG
QTc	QT Interval corrected
QTcF	QT Interval corrected (Fridericia's correction)
RX	Prescription
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SI	International System of Units
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
SST	serum separating tube
sUA	serum uric acid
TEAE	Treatment Emergent Adverse Event

Abbreviation	Description
TID	three times per day
TFL	Table, Figure and Listings
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures for the HZNP-KRY-201 study that will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

[redacted] will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings for the HZNP-KRY-201 study, including summaries of study concentrations for methotrexate (MTX) polyglutamate and Pegloticase and anti-drug antibodies. The details of summaries for pharmacokinetic (PK) parameters is not covered in the scope of this SAP and will be provided in a separate PK analysis plan.

[redacted] will provide summarizations and listings for safety reviews.

2.2. Timings of Analyses

The primary analysis of safety, efficacy and pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study. Additionally, data may be summarized after all subjects have completed 14 weeks of treatment in the Pegloticase + Immunomodulator (IMM) Period or discontinued therapy (or study) prior to that time, and after all subjects have completed 24 weeks of treatment in the Pegloticase + IMM Period or discontinued therapy (or study) prior to that time.

Additional summary of the data may be performed periodically throughout the study, and safety data will be summarized regularly for safety monitoring by the Sponsor.

3. Study Objectives

The overall objective of the study is to assess the efficacy, safety, tolerability, and PK of the concomitant use of pegloticase with MTX to enhance the response rate seen with pegloticase alone in adults with uncontrolled gout.

3.1. Primary Objective

The primary objective is to estimate the response rate during Month 6 (Weeks 20, 22, and 24), as measured by the sustained normalization of serum uric acid (sUA) to <6 mg/dL for at least 80% of the time during Month 6 in subjects receiving pegloticase with MTX.

3.2. Secondary Objectives

- Estimate the response rate during Month 3 (Weeks 10, 12 and 14), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 3 in subjects receiving pegloticase with MTX.
- Estimate the overall response rate, as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 3 (Weeks 10, 12 and 14) and Month 6 (Weeks 20, 22 and 24) combined in subjects receiving pegloticase with MTX.
- Estimate the 5 mg/dL response rate during Month 3, during Month 6, and Overall (Months 3 and 6 combined), as measured by the sustained normalization of sUA to <5 mg/dL for at least 80% of the time in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in sUA in subjects receiving pegloticase with MTX.

3.3. Exploratory Objectives

- Estimate the response rate during Month 9 (Weeks 32, 34 and 36), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 9 in subjects receiving pegloticase with MTX.
- Estimate the response rate during Month 12 (Weeks 48, 50 and 52), as measured by the sustained normalization of sUA to <6 mg/dL for at least 80% of the time during Month 12 in subjects receiving pegloticase with MTX.
- Estimate the 5 mg/dL response rate during Month 9 (Weeks 32, 34 and 36), as measured by the sustained normalization of sUA to <5 mg/dL for at least 80% of the time during Month 9 in subjects receiving pegloticase with MTX.
- Estimate the 5 mg/dL response rate during Month 12 (Weeks 48, 50 and 52), as measured by the sustained normalization of sUA to <5 mg/dL for at least 80% of the time during Month 12 in subjects receiving pegloticase with MTX.
- Estimate the time to first sUA >6 mg/dL in subjects receiving pegloticase with MTX.
- Estimate the time to two consecutive sUAs >6 mg/dL (stopping rule) in subjects receiving pegloticase with MTX.

- Estimate the mean change from baseline to Week 24, 36 and 52 in urate volume and gout erosions using dual-energy computed tomography (DECT) scan of the hands and feet in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline in number of joints affected by tophi in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in tender joint count (68 point scale) in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in swollen joint count (66 point scale) in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in the Health Assessment Questionnaire – Disability Index (HAQ-DI) in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in the HAQ pain score in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in the HAQ health score in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in patient global assessment of gout in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in physician global assessment of gout in subjects receiving pegloticase with MTX.
- Estimate the mean change from baseline to Weeks 14, 24, 36, and 52 in subject assessment of average, least, and worst joint pain in subjects receiving pegloticase with MTX.
- Estimate the proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36, and 52 in subjects receiving pegloticase with MTX.
- Assess the PK of pegloticase in subjects receiving concomitant MTX.
- Assess the incidence of anti-PEG and anti-Uricase IgG antibodies.

3.4. Safety and Tolerability Objectives

- Assess the incidence of infusion reactions (IRs), anaphylaxis, gout flares, cardiovascular events, and the adverse event (AE/SAE) profile overall and potentially attributed to the combination of pegloticase and MTX.

3.5. Brief Description

This study is a multicenter, open-label, efficacy and safety study of pegloticase in combination

with MTX in adult subjects with uncontrolled gout.

Prior to Amendment 2, the study design included: 1) a Screening Period, lasting up to 6 weeks, which includes a 4-week MTX Run-in Period; 2) a 24-week Dual Therapy Period (KRYSTEXXA + MTX); 3) an End-of-study (Week 24)/Early Termination Visit. The original protocol included a telephone or email contact 30 days after the last infusion. Amendment 1 included a safety Follow-up Phone/Email Visit 30 days after the last KRYSTEXXA infusion (if females of childbearing potential have not ovulated since taking the last dose of MTX, a urine pregnancy test will be required) and 5) a Phone/E-mail Visit will be conducted 3 months after MTX discontinuation to non-vasectomized males regarding partner pregnancy.

The study design for Amendment 2.0 includes: 1) up to a 2-week Screening Period (screening should be complete within 2 weeks prior to Week -4), 2) a 4-week MTX Run-in Period (Week –4 through Day 1); 3) a 52-week Pegloticase + IMM (Pegloticase + MTX) Period 4) a Safety Follow-up (Phone/Email/Site Visit) and 5) a 3 and 6 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) and continuing until prior to the Week 52 Visit. Subjects must be able to tolerate MTX at a dose of 15 mg during the MTX Run-in (Week -4 through Day 1) to be eligible to participate in the Pegloticase + IMM Period. Subjects who are unable to tolerate MTX at a dose of 15 mg during the MTX Run-in Period will be considered screen failures.

Subjects who take at least one dose of MTX and who are females of childbearing potential will receive a safety follow-up Phone Call/E-mail/Site Visit approximately 30 days after the last dose of MTX to verify at least one ovulatory cycle has occurred after the last dose of MTX. If the subject has not ovulated, a urine pregnancy test will be performed. Subjects, who receive at least one dose of MTX and who are non-vasectomized males, will be asked, 3 months after MTX discontinuation, regarding partner pregnancy.

All subjects who complete the Run-In Period 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.

During the Pegloticase + IMM Period, pegloticase 8 mg will be administered intravenously (IV) every 2 weeks from Day 1 through the Week 50 Visit for a total of 26 infusions; pegloticase will be administered after all pre-dose study visit assessments have been completed at each visit. The date and start and stop time of infusion will be recorded. Serum uric acid stopping rules will be applied: subjects with sUA level > 6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue treatment, complete the End of Pegloticase Infusion Visit procedures within 2 weeks and continue the subject visits according to the protocol (without treatment).

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

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

The Investigator will review the clinical status and individual subject treatment goals at Week 24, and the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of study/Early Termination Visit.

Serum samples for measurement of sUA levels will be collected at the Screening Visit (within 2 weeks prior to the first dose of MTX at Week -4), the Week -4 Visit (prior to the first dose of MTX), and the Week -2 Visit during the MTX Run-in Period; within 48 hours prior to each pegloticase infusion (except on Day 1 when only 1 pre-infusion sample is required) and after the end of each pegloticase infusion prior to discharge, from the Pegloticase + IMM Period through Week 24 and at Weeks 32, 34, 36, 48 and 50; within 48 hours prior to each pegloticase infusion at Weeks 26, 28, 30, 38, 40, 42, 44 and 46 during the Pegloticase + IMM Period; and at the at the End of Pegloticase Infusions Visit (if applicable); at the Week 52/End of study/Early Termination Visit and Month 3 and Month 6 Visits. Optional (subjects who agree to participate) visits for frequent sampling for additional non-infusion visit sUA sampling (random, morning preferred) will occur at Week 1 and Week 7. A subject with sUA level >6 mg/dL (based on the local or central laboratory) at 2 consecutive study visits, beginning with the Week 2 Visit, will be discontinued from pegloticase treatment and remain on study.

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

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

3.6. Determination of Sample Size

A sample size of approximately 12-16 subjects is planned for this study. The primary efficacy endpoint, the proportion of subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6 (Weeks 20, 22, and 24) of the Pegloticase + IMM Period, will be demonstrated to be statistically greater than 43.5% (proportion of responders during Month 6 in phase 3 studies), according to an exact test for proportions with a 5% type I error, if at least 10/13 (77%) responders are observed; in that case, the lower bound of a 95% confidence interval (CI) for the proportion of responders will be approximately 46%.

3.7. Treatment Assignment & Blinding

The study is open-label.

3.8. Administration of Study Medication

During the MTX Run-in Period, which begins 4 weeks prior to the first dose of pegloticase, subjects will take oral MTX at a dose of 15 mg weekly. Subjects will be instructed to take MTX weekly on the same day each week (if dosing more frequently than once in a day (i.e. twice per day (BID), or three times per day (TID)), the total MTX dose should be taken within 24 hours, preferably the same calendar day) and record the date and time of dose/s in the dosing

calendar. During the Pegloticase + IMM Period, MTX should be taken 1 to 3 days prior to pegloticase infusion; however, if a subject does not do so, MTX must be taken ≥ 60 minutes prior to pegloticase infusion. During the MTX Run-in Period, if a dose is missed, it should be taken as soon as it is remembered. If it is within 48 hours of the next scheduled dose, the subject will be instructed to skip the missed dose and resume at the next regularly scheduled time; thus, subjects will be instructed not to double a dose to make up for a missed dose if within 48 hours of the next dose. If a subject becomes unable to tolerate the prescribed dosage of MTX during the Pegloticase + IMM Period, the dosage may be decreased (see Protocol Section 9.4.6.3.2.2).

Subjects who enrolled under Amendment 1 (Version 2.0) of the protocol, who did not consent to Amendment 2 (Version 3.0), will receive 12 infusions during the Pegloticase + IMM Period at the same dose of 8 mg administered IV every 2 weeks. Subjects who enrolled to Version 3.0 or reconsented to Version 3 will receive pegloticase at the same dose of 8 mg administered IV every 2 weeks for a total of 26 infusions from Day 1 through Week 50, inclusive. The date and start and stop time of infusion including the flush will be recorded. Subjects will not be fasting on the day of infusion and will be encouraged to have a snack or normal meal before or after the infusion. All subjects will receive standardized prophylactic treatment to reduce the risk of acute gout flares, unless medically contraindicated or not tolerated, beginning ≥1 week before the first dose of pegloticase. Standardized IR prophylaxis consisting of pre-treatment with antihistamines, acetaminophen, and corticosteroids will accompany each infusion.

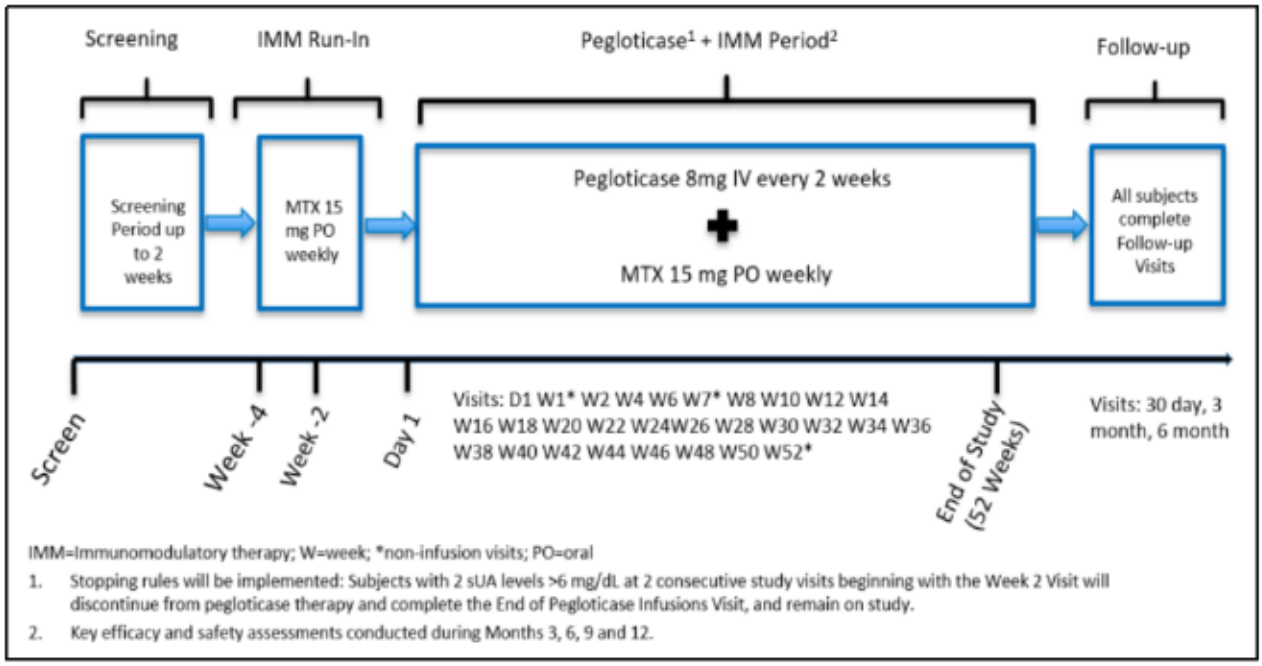
Subjects will take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the Week 52/End of Study/Early Termination Visit.

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

It is required that before a subject begins the Pegloticase + IMM Period, he or she has been taking at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤10 mg/day) for ≥1 week before the first dose of pegloticase and continues flare prophylaxis for the greater of 1) 6 months, 2) 3 months after achieving target serum urate (sUA < 6 mg/dL) for patients with no tophi detected on physical exam, or 3) 6 months after achieving target serum urate (sUA < 5 mg/dL) for patients with one or more tophi detected on initial physical exam that have since resolved.

3.9. Study Procedures and Flowchart

The flowchart copied from the protocol, Amendment 2, Section 2.1, is reproduced here.



IMM=Immunomodulatory therapy; W=week; *non-infusion visits; PO=oral

1. Stopping rules will be implemented: Subjects with 2 sUA levels >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue from pegloticase therapy and complete the End of Pegloticase Infusions Visit, and remain on study.
2. Key efficacy and safety assessments conducted during Months 3, 6, 9 and 12.

The schedule of assessments is copied from the protocol Amendment 2.

	Screening[1]/ MTX Run-in Period[2]			Pegloticase + IMM Period[3] Day 1 through Week 24														
	Screening Visit [4]	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 1 (±1 d)	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 7 (±1 d)	Wk 8 (±3 d)	Wk 10 (±3 d)	Wk 12 (±3 d)	Wk 14 (±3 d)	Wk 16 (±3 d)	Wk 18 (±3 d)	Wk 20 (±3 d)	Wk 22 (±3 d)	Wk 24 (±3 d)
Study Procedure/ Assessment				Inf 1		Inf 2	Inf 3	Inf 4		Inf 5	Inf 6	Inf 7	Inf 8	Inf 9	Inf 10	Inf 11	Inf 12	Inf 13
Informed consent	X																	
Enrollment				X														
Demographic data	X																	
Inclusion/exclusion criteria	X	X	X	X														
Medical/surgical history[5]	X	X																
Medication/substance use history[6]	X	X	X															
Physical examination[7]	X	X		X			X			X		X		X		X		X
Vital signs, height, and weight[8]	X	X		X		X	X	X		X	X	X	X	X	X	X	X	X
Electrocardiogram[9]				X														
HIV antibody screening	X																	

	Screening[1]/ MTX Run-in Period[2]			Pegloticase + IMM Period[3] Day 1 through Week 24													
	Screening Visit [4]	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 1 (±1 d)	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 7 (±1 d)	Wk 8 (±3 d)	Wk 10 (±3 d)	Wk 12 (±3 d)	Wk 14 (±3 d)	Wk 16 (±3 d)	Wk 18 (±3 d)	Wk 20 (±3 d)	Wk 22 (±3 d)	Wk 24 (±3 d)
Study Procedure/ Assessment				Inf 1		Inf 2	Inf 3	Inf 4		Inf 5	Inf 6	Inf 7	Inf 8	Inf 9	Inf 10	Inf 11	Inf 12	Inf 13
AE/SAE assessment[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Document gout flares and intensity	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X
Swollen/tender joint counts		X		X									X					X
HAQ	X	X		X									X					X
Patient global assessment	X	X		X									X					X
Physician global assessment	X	X		X									X					X
Joint pain assessment	X	X		X									X					X
DECT[11]				X														X
Tophi Assessment	X																	X
MTX dosing calendar		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MTX dispensed[12]		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X
MTX dosing[13]		Once weekly from Week -4 to the week 51, one week after the Week 50 Visit, inclusive																

	Screening[1]/ MTX Run-in Period[2]			Pegloticase + IMM Period[3] Day 1 through Week 24														
	Screening Visit [4]	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 1 (±1 d)	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 7 (±1 d)	Wk 8 (±3 d)	Wk 10 (±3 d)	Wk 12 (±3 d)	Wk 14 (±3 d)	Wk 16 (±3 d)	Wk 18 (±3 d)	Wk 20 (±3 d)	Wk 22 (±3 d)	Wk 24 (±3 d)
Study Procedure/ Assessment				Inf 1		Inf 2	Inf 3	Inf 4		Inf 5	Inf 6	Inf 7	Inf 8	Inf 9	Inf 10	Inf 11	Inf 12	Inf 13
Gout prophylaxis Rxs filled[14]		Rxs filled as needed																
Fexofenadine Rx filled[15]		Rx filled as needed																
Folic acid Rx filled[16]		Rx filled as needed																
MTX compliance/ reconciliation			X	X		X	X	X		X	X	X	X	X	X	X	X	X
Infusion reaction prophylaxis[17]				X		X	X	X		X	X	X	X	X	X	X	X	X
IR prophylaxis compliance (Yes/No)				X		X	X	X		X	X	X	X	X	X	X	X	X
Folic acid/gout flare prophylaxis compliance (Yes/No)			X	X		X	X	X		X	X	X	X	X	X	X	X	X
Pegloticase infusion				X		X	X	X		X	X	X	X	X	X	X	X	X
Pre-infusion MTX Polyglutamate sampling[18]				X			X			X							X	X
pegloticase PK sampling[19]				X	X	X	X	X	X	X	X		X		X		X	X

	Screening[1]/ MTX Run-in Period[2]			Pegloticase + IMM Period[3] Day 1 through Week 24													
	Screening Visit [4]	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 1 (±1 d)	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 7 (±1 d)	Wk 8 (±3 d)	Wk 10 (±3 d)	Wk 12 (±3 d)	Wk 14 (±3 d)	Wk 16 (±3 d)	Wk 18 (±3 d)	Wk 20 (±3 d)	Wk 22 (±3 d)	Wk 24 (±3 d)
Study Procedure/ Assessment				Inf 1		Inf 2	Inf 3	Inf 4		Inf 5	Inf 6	Inf 7	Inf 8	Inf 9	Inf 10	Inf 11	Inf 12	Inf 13
sUA[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X		X		X					X				X	X
Clinical chemistry	X	X	X	X		X		X					X				X	X
Spot urine collection	X	X	X	X		X		X					X				X	X
Antibody sample[21]				X	X	X	X	X	X	X	X		X		X		X	X
G6PD	X																	
Pregnancy test[22]	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X
Partner pregnancy[23]																		
Investigator assessment of clinical status[24]																		X

	Pegloticase + IMM Period[5] Week 26 through Week 50													End of Pegloticase Infusions Visit[25] (if applicable)	End of Study/ Early Termination	Safety Follow-up Phone/ Email Visit 30 Day	MTX Partner Pregnancy Follow-up	Post Treatment 3 and 6 month Follow-up[26]
	Wk 26 (±3 d)	Wk 28 (±3 d)	Wk 30 (±3 d)	Wk 32 (±3 d)	Wk 34 (±3 d)	Wk 36 (±3 d)	Wk 38 (±3 d)	Wk 40 (±3 d)	Wk 42 (±3 d)	Wk 44 (±3 d)	Wk 46 (±3 d)	Wk 48 (±3 d)	Wk 50 (±3 d)	Within 2 weeks following final infusion if prior to Wk 50	Wk 52 (±3 d)	30 days after last pegloticase infusion (±3 d)	approx. 3 months after last MTX dose	3 Month & 6 Month
Study Procedure/ Assessment	**Inf 14**	**Inf 15**	**Inf 16**	**Inf 17**	**Inf 18**	**Inf 19**	**Inf 20**	**Inf 21**	**Inf 22**	**Inf 23**	**Inf 24**	**Inf 25**	**Inf 26**					
Physical examination[7]						X								X	X			X
Vital signs, height, and weight[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
AE/SAE assessment[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Document gout flares and intensity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Swollen/tender joint counts						X								X	X			X
HAQ						X								X	X			X
Patient global assessment						X								X	X			X
Physician global assessment						X								X	X			X
Joint pain assessment						X								X	X			X

	Pegloticase + IMM Period[3] Week 26 through Week 50													End of Pegloticase Infusions Visit[25] (if applicable)	End of Study/ Early Termination	Safety Follow-up Phone/ Email Visit 30 Day	MTX Partner Pregnancy Follow-up	Post Treatment 3 and 6 month Follow-up[26]
	Wk 26 (±3 d)	Wk 28 (±3 d)	Wk 30 (±3 d)	Wk 32 (±3 d)	Wk 34 (±3 d)	Wk 36 (±3 d)	Wk 38 (±3 d)	Wk 40 (±3 d)	Wk 42 (±3 d)	Wk 44 (±3 d)	Wk 46 (±3 d)	Wk 48 (±3 d)	Wk 50 (±3 d)	Within 2 weeks following final infusion if prior to Wk 50	Wk 52 (±3 d)	30 days after last pegloticase infusion (±3 d)	approx. 3 months after last MTX dose	3 Month & 6 Month
Study Procedure/ Assessment	**Inf 14**	**Inf 15**	**Inf 16**	**Inf 17**	**Inf 18**	**Inf 19**	**Inf 20**	**Inf 21**	**Inf 22**	**Inf 23**	**Inf 24**	**Inf 25**	**Inf 26**					
DECT[11]						X								X	X			
Tophi Assessment						X								X	X			X
Dispense MTX dosing calendar	X	X	X	X	X	X	X	X	X	X	X	X	X					
MTX dispensed[12]	X	X	X	X	X	X	X	X	X	X	X	X	X					
MTX dosing[13]	Once weekly from Week -4 to the week 51, one week after the Week 50 Visit, inclusive																	
Gout prophylaxis Rxs filled[14]	Rxs filled as needed																	
Fexofenadine Rx filled[15]	Rxs filled as needed																	
Folic acid Rx filled[16]	Rxs filled as needed																	
MTX compliance/ reconciliation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Infusion reaction prophylaxis[17]	X	X	X	X	X	X	X	X	X	X	X	X	X					

	Pegloticase + IMM Period[3] Week 26 through Week 50													End of Pegloticase Infusions Visit[25] (if applicable)	End of Study/ Early Termination	Safety Follow-up Phone/ Email Visit 30 Day	MTX Partner Pregnancy Follow-up	Post Treatment 3 and 6 month Follow-up[26]
	Wk 26 (±3 d)	Wk 28 (±3 d)	Wk 30 (±3 d)	Wk 32 (±3 d)	Wk 34 (±3 d)	Wk 36 (±3 d)	Wk 38 (±3 d)	Wk 40 (±3 d)	Wk 42 (±3 d)	Wk 44 (±3 d)	Wk 46 (±3 d)	Wk 48 (±3 d)	Wk 50 (±3 d)	Within 2 weeks following final infusion if prior to Wk 50	Wk 52 (±3 d)	30 days after last pegloticase infusion (±3 d)	approx. 3 months after last MTX dose	3 Month & 6 Month
Study Procedure/ Assessment	**Inf 14**	**Inf 15**	**Inf 16**	**Inf 17**	**Inf 18**	**Inf 19**	**Inf 20**	**Inf 21**	**Inf 22**	**Inf 23**	**Inf 24**	**Inf 25**	**Inf 26**					
IR prophylaxis compliance (Yes/No)	X	X	X	X	X	X	X	X	X	X	X	X	X					
Folic acid/gout flare prophylaxis compliance (Yes/No)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Pegloticase infusion	X	X	X	X	X	X	X	X	X	X	X	X	X					
Pre-infusion MTX Polyglutamate sampling[18]						X												
Pegloticase PK sampling[19]						X								X	X			
sUA[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Hematology						X								X	X			X
Clinical chemistry						X								X	X			X
Spot urine collection						X								X	X			
Antibody sample[21]						X								X	X			X
Pregnancy test[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Pegloticase + IMM Period[3] Week 26 through Week 50													End of Pegloticase Infusions Visit[25] (if applicable)	End of Study/ Early Termination	Safety Follow-up Phone/ Email Visit 30 Day	MTX Partner Pregnancy Follow-up	Post Treatment 3 and 6 month Follow-up[26]
	Wk 26 (±3 d)	Wk 28 (±3 d)	Wk 30 (±3 d)	Wk 32 (±3 d)	Wk 34 (±3 d)	Wk 36 (±3 d)	Wk 38 (±3 d)	Wk 40 (±3 d)	Wk 42 (±3 d)	Wk 44 (±3 d)	Wk 46 (±3 d)	Wk 48 (±3 d)	Wk 50 (±3 d)	Within 2 weeks following final infusion if prior to Wk 50	Wk 52 (±3 d)	30 days after last pegloticase infusion (±3 d)	approx. 3 months after last MTX dose	3 Month & 6 Month
Study Procedure/ Assessment	**Inf 14**	**Inf 15**	**Inf 16**	**Inf 17**	**Inf 18**	**Inf 19**	**Inf 20**	**Inf 21**	**Inf 22**	**Inf 23**	**Inf 24**	**Inf 25**	**Inf 26**					
Partner pregnancy[23]																	X	
Investigator Assessment of Clinical Status[24]														X	X			

AE = adverse event; d = day(s); DECT = dual-energy computed tomography; G6PD = glucose-6-phosphate dehydrogenase; HAQ = Health Assessment Questionnaire; HIV = human immunodeficiency virus; IR = infusion reaction; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; PK = pharmacokinetic; Rx = prescription; sUA = serum uric acid; V= Visit; wk(s) = week(s); IMM = Immunomodulator

Footnotes:

1. The Screening Period is inclusive of the MTX Run-in Period.
2. During the MTX Run-in Period, subjects will take oral MTX 15 mg weekly, which begins 4 weeks prior to the first dose of pegloticase. Subjects unable to tolerate 15 mg of MTX during the Run-in period will be considered screen failures.
3. It is recommended that before a subject begins the Pegloticase + IMM Period, he or she has been taking the per protocol standard gout flare prophylaxis regimen for ≥1 week prior to pegloticase infusion. During the Pegloticase + IMM Period subjects will continue taking MTX weekly inclusive of Week 51 (1 week after the last pegloticase infusion). Subjects will receive pegloticase infusions every 2 weeks Day 1 through Week 50.
4. The Week -6 Visit is designated the Screening Visit and can occur any time within 2 weeks prior to the first dose of MTX at Week -4.
5. The Investigator or designee will collect a complete gout history and other relevant medical/surgical history.
6. Medication history (i.e., prior medications) will include gout medications, starting at the time of diagnosis and up to (but not including) the Day 1 Visit; substance use history; History of all prior gout medications will be collected. History of non-gout medication use in the year prior to Screening will be collected.
7. A complete physical examination will be performed at the Screening Visit and will include assessments of for presence of tophi, as well as gout history and symptom severity. A targeted physical examination (includes heart, lungs and abdominal exam and exam for joint and skin evaluation and assessment of AEs) will be conducted based on potential risk for or occurrence of AEs at Week -4, Day 1, and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20, 24, 36, Week 52/End of Study/Early Termination and Post Treatment 3 and 6 month Follow-up Visits. Clinically significant findings from the targeted physical examinations will be recorded as AEs. At Weeks

24 and 36, Week 52/End of Study/Early Termination and Post Treatment 3 and 6 month Follow-up Visits, an assessment for presence of tophi will be conducted during the targeted physical examination.

8. Heart rate and blood pressure measurements should be taken after the subject has been in a sitting position and in a rested and calm state for at least 5 minutes and, for study visits during the Pegloticase + IMM Period, before the pegloticase infusion and any time after the end of the infusion, but prior to subject's discharge/release from the site. Weight should be measured in kilograms or pounds without shoes and recorded at Screening Visit; prior to pegloticase infusions on Day 1 and at the Week 8, 16, 24, 36, the End of Pegloticase Treatment, at the Week 52/End-of-study/Early Termination Visit and the Post Treatment 3 and 6 month follow-up visits. Height will be collected at the Screening Visit only.
9. Electrocardiogram should be completed prior to the pegloticase infusion at Day 1 Visit.
10. AEs/SAEs will be collected from signature of the ICF. Serious AEs will be captured/monitored at the Safety Follow-up Phone/Email/Site Visit 30 days after the last dose of MTX. At the Safety Follow-up Phone/Email/Site Visit, females of childbearing potential will be asked to confirm if ovulation has occurred since the last dose of MTX. If the subject had not ovulated, a urine pregnancy test will be required. AEs/SAEs will collected until the 6 month Post Treatment Follow-up Visit. For each AE, Investigators will be record if the event was possibly an infusion reaction or anaphylaxis and if so, will be prompted to complete additional CRFs.
11. For sites with DECT capability, DECT will be obtained at Day 1 and Weeks 14, 24 and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination. The DECT may be completed within +/- 5 days of the scheduled timepoint. Subjects who end pegloticase infusions prior to Week 52 should follow the scheduled timepoints but avoid a repeat DECT scan within 6 weeks of a prior scan.
12. MTX will be dispensed and brought back at each visit to check compliance. If subjects require a MTX dose reduction, the Investigator will prescribe the subject the number of tablets to take weekly. The updated number of tablets along with the date and time of each MTX dose should be recorded in the dosing calendar.
13. MTX should be taken 1 to 3 days prior to pegloticase infusion; however, if a subject does not do so, MTX must be taken ≥60 minutes prior to pegloticase infusion.
14. For gout prophylaxis, subjects are required to take at least one protocol standard gout flare prophylaxis regimen (i.e. colchicine and/or non-steroidal anti-inflammatory drugs and/or low-dose prednisone ≤10 mg/day) for ≥1 week before the first dose of pegloticase and continues flare prophylaxis per American College of Rheumatology guidelines [Khanna D et al.2012] for the greater of 1) 6 months, 2) 3 months after achieving target serum urate (sUA < 6 mg/dL) for patients with no tophi detected on physical exam, or 3) 6 months after achieving target serum urate (sUA < 5 mg/dL) for patients with one or more tophi detected on initial physical exam that have since resolved. For IR prophylaxis, fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) will be taken the day before each infusion; fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) given over the infusion duration 10-30 minutes (recommended) or hydrocortisone (200 mg IV) will be administered immediately prior to each infusion. given over the infusion duration 10-30 minutes will be administered immediately prior to each infusion.
15. For IR prophylaxis, fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) will be taken the day before each infusion.
16. Subjects will take folic acid 1 mg orally every day beginning at Week -4 (the start of MTX) until prior to the Week 52/End of Study/Early Termination Visit during the Pegloticase + IMM Period.
17. Infusion reaction prophylaxis includes fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) administered the day before each infusion; fexofenadine (60 mg or 180 mg orally based on the Principal Investigator's discretion) and acetaminophen (1000 mg orally) administered on the morning of each infusion; and methylprednisolone (125 mg IV) given over the infusion duration 10-30 minutes (recommended) or hydrocortisone (200 mg IV) will be administered immediately prior to each infusion. administered immediately prior to each infusion.
18. Blood samples will be collected prior to pegloticase infusion on Day 1 and at Weeks 4, 8, 22, 24 and 36 during the Pegloticase + IMM Period for MTX Polyglutamate levels.
19. For all subjects, serum samples for PK analysis will be collected prior to pegloticase infusion and after the end of infusion (prior to discharge) on Day 1 and at the Weeks 2, 4, 6, 8 and 36 Visits and prior to pegloticase infusion only at the Weeks 10, 14, 18, 22, 24; at the End of Pegloticase Infusions Visit (if applicable); and Week 52/End-of-Study/Early Termination Visit. Visits for frequent sampling of a subset of subjects who consent for additional non-infusion visit PK sampling (random, morning preferred) will occur at Week 1 and Week 7.
20. Serum samples for measurement of sUA levels will be collected at the Screening Visit (within 2 weeks prior to the first dose of MTX at Week -4), the Week -4 Visit (prior to the first dose of MTX), and the Week -2 Visit; within 48 hours prior to each pegloticase infusion (except on Day 1 when only 1 pre-infusion sample is required and will be drawn at the site just prior to the infusion); and after the end of each pegloticase infusion prior to discharge, from the Pegloticase + IMM Period through week 24 and at Weeks 32, 34, 36, 48 and 50; within 48 hours prior to each pegloticase infusion at Weeks 26, 28, 30, 38, 40, 42, 44 and 46 during the Pegloticase + IMM Period; and at the at the End of Pegloticase Infusions Visit (if applicable); at the Week 52/End of study/Early Termination Visit and Month 3 and Month 6 Visits. Visits for frequent sampling of a

subset of subjects who consent for additional non-infusion visit PK sampling (random, morning preferred) will occur at Week 1 and Week 7. Two separate samples/tubes of blood should be collected within 48 hours prior to the pegloticase infusion (except on Day1 when only 1 pre-infusion sample is required for the central laboratory). One sample/tube will be assessed by the site's local laboratory to be used for on-study subject management; pre-infusion sUA results must be reported by the local or central laboratory prior to each pegloticase infusion. If a local laboratory sample is drawn (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit. The second sample/tube will be sent to the central laboratory for analysis and recording in the database. See the Laboratory Manual for instructions for alternate scenarios. A subject with sUA level >6 mg/dL (based on the local or central laboratory) at 2 consecutive study visits, beginning with the Week 2 Visit, will be classified as a non-responder and subjects will complete the End of Pegloticase Treatment Visit. The subject will continue on study (without treatment).

21. Serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 2, 4, 6, 8, 10, 14, 18, 22, 24, 36, if applicable the End of Pegloticase Infusions Visit and Week 52/End of Study/Early Termination Visits and at the 3 Month Post Treatment Visit. Visits for frequent sampling of a subset of subjects who consent for additional non-infusion visit PK sampling (random, morning preferred) will occur at Week 1 and Week 7. In the event of an AE suspected to be an infusion reaction, a serum sample will be collected at that time or at the subsequent visit for evaluation of pegloticase antibodies.
22. For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit. A urine pregnancy test will be performed at each visit until 30 days after the last MTX dose if the subject has not ovulated; at the End of Pegloticase Infusions Visit (if applicable), the Week 52/End of study/Early Termination Visit procedures and at the 30 day follow up phone/e-mail/site visit it is determined that the subject has not ovulated since the last dose of MTX; a urine pregnancy test will be performed at all other indicated visits.
23. Subjects who are non-vasectomized males will be asked 3 months after MTX discontinuation regarding partner pregnancy. This will occur at a regulatory scheduled visit or by a separate phone/email/site visit.
24. The Investigator will review the clinical status of the subject at the Week 24 Visit and the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of study/Early Termination Visit.
25. Subjects who end treatment due to the stopping rules or other reasons should complete the End of Pegloticase Treatment Visit within 2 weeks of the last infusion. Subjects should remain on study. See Protocol Section 9.5.6.3 for details on visits and procedures.
26. Subjects will return to the site 3 months and 6 months following their final infusion for follow-up procedures.

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4. Endpoints

4.1. Primary Efficacy Endpoint

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

4.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The proportion of Month 3 (Weeks 10, 12, and 14) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 3.
- The proportion of overall responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 3 (Weeks 10, 12 and 14) and Month 6 (Weeks 20, 22 and 24) combined.
- The proportion of 5 mg/dL responders during Month 3, during Month 6, and overall (Months 3 and 6 combined), defined as subjects achieving and maintaining sUA < 5 mg/dL for at least 80% of the time during each timepoint.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in sUA.

4.3. Exploratory Endpoints

The exploratory efficacy endpoints are:

- The proportion of Month 9 (Weeks 32, 34 and 36) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 9.
- The proportion of Month 12 (Weeks 48, 50 and 52) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 12.
- The proportion of Month 9 (Weeks 32, 34 and 36) 5 mg/dL responders, defined as subjects achieving and maintaining sUA <5 mg/dL for at least 80% of the time during Month 9.
- The proportion of Month 12 (Weeks 48, 50 and 52) 5 mg/dL responders, defined as subjects achieving and maintaining sUA <5 mg/dL for at least 80% of the time during Month 12.
- The time to first pre-infusion sUA > 6 mg/dL in subjects receiving pegloticase with MTX.
- The time to two consecutive pre-infusion sUAs > 6 mg/dL (stopping rule) in subjects receiving pegloticase with MTX.
- The mean change from baseline to Weeks 24, 36, and 52 in urate volume and bone erosions due to gout using DECT.
- The mean change from baseline in number of joints affected by tophi
- The mean change from baseline to Weeks 14, 24, 36, and 52 in tender joint count (68 point scale).

- The mean change from baseline to Weeks 14, 24, 36, and 52 in swollen joint count (66 point scale).
- The mean change from baseline to Weeks 14, 24, 36, and 52 in HAQ-DI.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in HAQ pain score.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in HAQ health score.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in patient global assessment of gout.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in physician global assessment of gout.
- The mean change from baseline to Weeks 14, 24, 36, and 52 in subject assessment of average, least, and worst joint pain.
- The proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36, and 52.

4.4. Pharmacokinetic and Anti-drug Antibody Endpoints

The PK and anti-drug antibody endpoints are:

- PK of pegloticase in subjects receiving concomitant MTX.
- Incidence of anti-PEG and anti-Uricase IgG antibodies.

4.5. Safety and Tolerability Endpoints

Safety and tolerability endpoints are:

- Incidence of IRs, anaphylaxis, gout flares, cardiovascular events, and the AE/SAE profile overall, and potentially attributed to the combination of pegloticase and MTX.

5. Analysis Populations

The following analysis populations will be defined for this study:

5.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all enrolled subjects who take at least one dose of MTX.

The ITT will be used for efficacy analyses and safety analyses.

5.2. Modified Intention-to-Treat Population

The Modified Intention-to-Treat (mITT) population will include all enrolled subjects who receive at least 1 dose of pegloticase.

The mITT population will be used for efficacy analyses and safety analyses.

If the mITT population and ITT population are identical, the summaries will be performed only for the mITT population.

5.3. Pharmacokinetic Population

The Pharmacokinetic (PK) Population will include all enrolled subjects who receive at least 1 dose of pegloticase and have a post-pegloticase sample evaluable for PK analysis.

The PK population will be used for all pharmacokinetic analyses.

5.4. Protocol Deviations

Protocol deviations are entered into the eCRF system. Deviations will be categorized as major or minor. Deviations will be classified as occurring in the Screening, MTX Run-in Period, Pegloticase + IMM Period, or Follow-up Period. Using the ITT, mITT, and PK population, major deviations will be summarized by type and period of occurrence.

6. General Aspects for Statistical Analysis

6.1. General Methods

The following conventions will be utilized in the analyses:

- In general, descriptive summaries will be provided. Efficacy summaries will be provided showing columns for both the ITT and mITT population. Safety summaries will be provided for the ITT and mITT population. If the ITT population and mITT population are identical, then only the mITT population summaries will be produced.
- The following column labels will be used: "ITT Population", "mITT Population", or "PK Population". If a summary table is applicable to a single population, the population will be stated in the summarization column.
- Unless otherwise indicated, continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.
- The same number of decimal places as the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.
- Unless specified, confidence intervals (CI) will be based on 95% confidence and two-sided.
- If multiple assessments occur at a given time point, the latest value will be used.
- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.
- Additional programming considerations are provided in Section 12.

6.2. Key Definitions

6.2.1. Baseline

Two different baseline values will be defined.

The first baseline value will be defined as the last measurement taken prior to first dosing of MTX in the MTX Run-in Period (considering unscheduled visits when available). This baseline will be referred to as the MTX baseline. Change from MTX Baseline will be defined as the measurement at each time point minus the Baseline value. The MTX baseline will be defined for all assessments, including sUA, DECT assessments, joints affected by tophi, tender joint counts, swollen joint counts, patient global assessment, physician global assessment, subject assessment of pain associated with gout, GCR, laboratory results, vital signs, and electrocardiograms.

The second baseline value, to be used in the assessments of change from baseline in sUA, HAQ-DI, HAQ-Health score, HAQ-pain score, patient global assessment, physician global assessment, tender joint count, and swollen joint count, will be defined as the last measurement taken prior to the first infusion of the pegloticase in the Pegloticase + IMM period. This baseline

will be referred to as the pegloticase baseline. Change from pegloticase baseline will be defined as the measurement at each time point minus the baseline value.

6.2.2. Study Day

Two different study days will be calculated. The first study day will be determined relative to the first dose of MTX in the MTX Run-in Period. The second 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. There will be no study day 0.

6.2.3. Age

Age will be calculated as (informed consent date - date of birth + 1) / 365.25 and truncated to complete years. If the date of birth is only partially available, the first of the month will be imputed for any missing days and January will be imputed for any missing months.

6.3. Missing Data

6.3.1. 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 + IMM 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 + IMM 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.

6.3.2. 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 + IMM Period. Imputed dates will not appear in the data listings.

For partial start dates:

- If the month and year of adverse event onset 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 + IMM 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 + IMM 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 + IMM 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 + IMM 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 + IMM 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 + IMM 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 + IMM 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 MTX + IMM period will be considered "related" to Methotrexate and "related" to pegloticase for statistical summaries.

Missing severities will be considered "severe" for statistical summaries.

6.4. Visit Windows

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 Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6 below. Table 1 shows windows for the vital sign assessments, gout assessments, and sUA collections. Table 2 shows windows for the clinical laboratory assessments. Table 3 shows the windows for swollen/tender joints, HAQ, patient and clinician global assessment parameters, joint pain assessments. Table 4 shows the windows for the assessment of DECT and the number of joints affected by tophi. Table 5 show windows for pre-infusion MTX polyglutamate PK assessments. Table 6 shows windows for pegloticase PK assessments. Unscheduled sUA visits, assessed by the central laboratory or local laboratory (see Section 9.1), will be assigned an analysis window according to the window below. These unscheduled will be used for the determination of sUA responder.

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

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase + IMM	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 – 176
	Week 26	183	177 – 190
	Week 28	197	191 – 204
	Week 30	211	205 – 218
	Week 32	225	219 – 232
	Week 34	239	233 – 246
	Week 36	253	247 – 260
	Week 38	267	261 – 274
	Week 40	281	275 – 288
	Week 42	295	289 – 302
	Week 44	309	303 – 316
	Week 46	323	317 – 330
	Week 48	337	331 – 344
	Week 50	351	345 – 358
	Week 52	365	≥ 359

[a] Study days in the Pegloticase + IMM 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)

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

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
	Week 24	169	163 - 211
	Week 36	253	212 - 309
	Week 52	365	≥ 310

[a] Study days in the Pegloticase + IMM 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 (Swollen/Tender Joint Counts, HAQ, Patient and Clinician Global Assessments, Joint Pain)

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase + IMM	Day 1	1	1
	Week 14	99	2 – 134
	Week 24	169	135 – 211
	Week 36	253	212 – 309
	Week 52	365	≥ 310

[a] Study days in the Pegloticase + IMM 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 (DECT and Joints Affected by Tophi)

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase + IMM	Day 1	1	1
	Week 24	169	2 – 211
	Week 36	253	212 – 309
	Week 52	365	≥ 310

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

Table 5: 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 + IMM	Day 1	1	1
	Week 4	29	2 – 43
	Week 8	57	44 – 106

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
	Week 22	155	107 – 162
	Week 24	169	163 – 211
	Week 36	253	≥ 212

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

Table 6: Visit Windows for Assigning ET and End of Pegloticase Visits to a Scheduled Visit (Pegloticase PK)

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase + IMM	Day 1	1	1
	Week 1	8	2 – 11
	Week 2	15	12 – 22
	Week 4	29	23 – 36
	Week 6	43	37 – 46
	Week 7	50	47 – 53
	Week 8	57	54 – 64
	Week 10	71	65 – 85
	Week 14	99	86 – 113
	Week 18	127	114 – 141
	Week 22	155	142 – 162
	Week 24	169	163 – 211
	Week 36	253	212 – 309
	Week 52	365	≥ 310

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

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.

For visit summaries and changes from baseline summaries, ET and End of Pegloticase visits will also be summarized separately, in addition to the visit to which it was windowed, for summaries by visit.

6.5. Pooling of Centers

Data from all sites will be summarized together for analyses.

6.6. Subgroups

No subgroup analyses are planned for the study.

7. Subject Disposition

A summary of subject disposition will be provided including the number of subjects screened and number of screen failures (received MTX or did not receive MTX), as well as the number of subjects in each analysis population (ITT, mITT, and PK Populations). In addition, the number and percent of subjects in each of the following categories will be provided:

- Entered the MTX Run-in Period
- Completed the MTX Run-in Period
- Discontinued early from the MTX Run-in Period (noting all subjects in the mITT will have completed the MTX Run-in Period by definition) along with Primary Reason for Discontinuation from Run-In Period.
- Entered the Pegloticase + IMM Period
    - Completed Treatment
    - Completed treatment at Week 24 (Amendment 1)
    - Completed treatment at the 52 Week (Amendment 2)
    - Discontinued Prematurely from the Pegloticase + IMM Period along with Reason for treatment discontinuation
    - Completed Study
    - Completed the study at Week 24 (Amendment 1)
    - Completed the study at Week 52 (Amendment 2)
    - Discontinued Prematurely from the study in Pegloticase + IMM Period along with reason for study discontinuation in the Pegloticase + IMM Period
- Have 3 month follow-up
- Have 6 month follow-up

Percentages will be based on the number of subjects in each population.

A separate summary will be provided of the number and percentage of subjects attending each visit using the ITT, mITT, and PK Populations. Percentages will be based on the number of subjects in the population summarized. Counts and percentages will not be presented for the discontinuations in the Pegloticase + IMM period for the ITT population. ITT population subjects who received an infusion of Pegloticase are also included in the mITT population.

A summary of subjects, with scheduled visits completed, will be presented for the ITT, mITT, and PK population. Percentages will be based on the number of subjects in the population summarized.

8. Demographics, Other Characteristics, and Medication

8.1. Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented overall for the ITT Population, mITT Population, and PK Population. The characteristics being summarized include: age, age category (18-40 years, >40-65 years), sex, race, ethnicity, time since first symptoms of gout (in years), time since first diagnosis of gout (in years), number of gout flares in joints over the past 12 months, occurrences of overnight stays in the hospital due to gout prior to screening, prior occurrence of tophi, prior occurrence of kidney stones, kidney function affected by gout historically, tobacco use history, current tobacco use status, alcohol use, other substance use, baseline weight, baseline height, baseline body mass index (BMI), baseline body surface area (BSA). Age, time since first symptoms of gout, time since first diagnosis of gout, number of gout flares over the past 12 months, baseline weight, baseline height, baseline BMA, and baseline BSA will be summarized as continuous variables showing number of non-missing values, mean, standard deviation, median, minimum and maximum. Age category, sex, race, occurrences of overnight stays in the hospital due to gout, prior occurrence of tophi, prior occurrence of kidney stones, kidney function affected by gout, the urate lowering therapy history (allopurinol history, feboxustat history, and other urate-lowering therapies, which are from the investigator assessment of clinical status form), tobacco use history, current tobacco use status, alcohol use, and other substance use will be summarized using categorical values.

Weight will be converted to kilograms (kg) when reported in pounds (lbs) as follows: Weight (in kg) = weight (in lbs) * 0.4536

BMI will be calculated as Weight (kg) / Height $(m)^2$.

Time since first gout symptoms will be calculated as: (informed consent date - date of first symptoms + 1) / 365.25, rounded to two decimal places. In the event of a partial first symptom date, the earliest possible date implied by the data provided will be imputed.

Time since first gout diagnosis will be calculated as: (informed consent date - date of first diagnosis + 1) / 365.25, rounded to two decimal places. In the event of a partial diagnosis date, the earliest possible date implied by the data provided will be imputed.

Demographic data and baseline characteristics will be provided in subject listings.

8.2. Medical History and Concomitant Diseases

Medical history information will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1, summarized and presented overall for the ITT, and MITT Populations. Summaries will be ordered alphabetically by system organ class (SOC) and then, within a SOC, alphabetically by preferred term (PT).

Medical history data will be listed.

8.3. Medication

Medications will be coded using WHODrug Global B3 September 2018 dictionary. Prior medications, concomitant medications used during the MTX Run-in Period, and concomitant medication used in the Pegloticase + IMM Period will be summarized by presenting the counts and percentage of subjects using medications overall for the ITT and mITT Populations.

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 mITT Populations. Subjects will be counted only once for each medication class and each preferred drug name.

Prior medications, concomitant medications, and medications during follow-up period will be listed together with a designation to identify the period(s) of usage and sorted by start date. For determination of period(s) of use, missing date imputation rules are provided in Section 6.3.1.

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):

Medication Start Date	Medication End Date	Prior	Concomitant in MTX Run-in Period	Concomitant in Pegloticase Treatment Period	Follow-up (> 30 days of either End of Pegloticase or Week 52 Visits)
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 pegloticase/MTX dose	Yes	Yes	Yes	No
Unknown	> 30 days after last pegloticase/MTX dose t	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

  - Those started 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 + IMM 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 + IMM 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 infusion.
- A medication with a start date prior to the first infusion date of pegloticase in the Pegloticase + IMM Period with a stop date strictly after the first infusion date of pegloticase in the Pegloticase + IMM Period.
- A medication with a start date prior to the first infusion date of pegloticase in the Pegloticase + IMM 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 + IMM 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 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

As such, the same medication may be summarized in one or more of prior, concomitant in the MTX Run-in Period, or concomitant in the Pegloticase + IMM Period, or in the Follow-up Period. The summary tables will not be mutually exclusive. Missing date imputation rules are provided in Section 6.3.1.

For the ITT population, prior medications and concomitant medications in the MTX Run-in Period will be summarized. For the mITT population, prior medications, concomitant medications in the MTX Run-in Period, concomitant medications in the Pegloticase + IMM Period, and medications in the Follow-up Period will be summarized. In addition, for the mITT population, medications used for gout treatment after the last pegloticase infusion will be summarized.

8.3.1. Concomitant Procedures

A listing will be provided for concomitant procedures the subject underwent during the study. No other analysis is planned for concomitant procedures.

9. Efficacy

9.1. Handling Rules for sUA Values

Serum samples for measurement of sUA levels are scheduled for collection at the Screening Visit (within 2 weeks prior to the first dose of MTX at Week -4), the Week -4 Visit (prior to the first dose of MTX), and the Week -2 Visit; within 48 hours prior to each pegloticase infusion (except on Day 1 when only 1 pre-infusion sample is required and will be drawn at the site just prior to the infusion); and after the end of each pegloticase infusion prior to discharge, from the Pegloticase + IMM Period through week 24 and at Weeks 32, 34, 36, 48 and 50; within 48 hours prior to each pegloticase infusion at Weeks 26, 28, 30, 38, 40, 42, 44 and 46 during the Pegloticase + IMM Period; and at the at the End of Pegloticase Infusions Visit (if applicable); at the Week 52/End of study/Early Termination Visit and Month 3 and Month 6 Visits. Visits for frequent sampling of a subset of subjects who consent for additional non-infusion visit PK sampling (random, morning preferred) will occur at Week 1 and Week 7, which will be considered as pre-infusion.

- 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 the lab assay's limit of quantification (e.g. "<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 a certain value of quantification (e.g. ">8.7"), the numeric value (e.g. 8.7) after '>' is used for the purpose of determining response and for summaries of observed values and the change from baseline.

9.2. Primary Efficacy Endpoint and Analysis

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

The sUA time curve will be used to estimate the proportion of time that the sUA is < 6 mg/dl using the available pre-infusion and post-infusion samples with non-missing sUA values.

The Month 6 period will include pre-infusion and post-infusion results at Week 20, pre-infusion and post-infusion results at Week 22, pre-infusion results at Week 24, and unscheduled pre-infusion assessments of sUA collected between Week 20 and Week 24 processed by the central laboratory. Section 9.1 shows the rules for inclusion of sUA values reported by local laboratories.

A robust estimate of proportion of time the sUA < 6 mg/dL can be determined by connecting a subject's neighboring data points with a straight line. If the sUA curve goes from below 6 mg/dL to above 6 mg/dL, linear interpolation will be used to estimate the time at which the sUA curve

intersects 6 mg/dL, using the last sample collected that was < 6 mg/dL and the first sample that was > 6 mg/dL. Analgously, if the sUA curve goes from above 6 mg/dL to below 6 mg/dL, linear interpolation will be used to estimate the time at which the sUA curve intersects 6 mg/dL, using the last sample that was above 6 mg/dL and the first value < 6 mg/dL after the SUA had been above 6 mg/dL

There will be no imputation of sUA values due to missed collections among those collected between Week 20 and Week 24. Only observed values will be included in the calculation. If a subject does not receive a pegloticase infusion at visits during Month 6 but has sUA results at those visits, those sUA results will be used in the calculation of response.

Let T1 = the number of elapsed hours between the first and last non-missing sUA concentration among those collected between Week 20 and Week 24 collections.
Let W1 = the number of hours among the T1 hours where the sUA concentration was below 6 mg/dL.

The proportion of hours $P = 100 * \frac{W1}{T1}$

If the subject's proportion of hours, P, is greater than or equal to 80% the subject will be called a responder for the primary efficacy endpoint. Subjects meeting the stopping rule, i.e. the subject has pre-infusion sUA values greater than 6 mg/dL at 2 consecutive scheduled visits (starting at Week 2) through Week 24, will be counted as non-responders. If only one sUA result is collected during Month 6 period, response will be based on the single value being strictly < 6 mg/dL. A subject with the proportion of hours, P, less than 80% will be counted as non-responders. Any other subject will be counted as a non-responder if sUA values are not collected during the Month 6 period.

This endpoint will be analyzed for the ITT and mITT populations. By definition, a subject who is in the ITT but not the mITT population will be counted as a non-responder for the primary efficacy endpoint for the ITT population, as they will not have sUA values beyond Day 1. The mITT analysis will be considered the primary analysis for this endpoint.

The proportion of hours during the period where the sUA was less than 6 mg/dL will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). The number and proportion of subjects that discontinued treatment due to the stopping rule will be summarized. The number and proportion of responders will be summarized along with a 95% exact (Clopper-Pearson) CI for the proportion.

9.3. Secondary Efficacy Endpoints and Analyses

9.3.1. Proportion of Month 3 Responders

The proportion of Month 3 (Weeks 10, 12, 14) responders, will be defined as subjects achieving and maintaining sUA < 6 mg/dL for at least 80% of the time during Month 3.

This endpoint will be analyzed for the ITT and mITT populations. The mITT analysis will be considered the primary analysis for this endpoint.

This determination will be completed using the same linear interpolation method described for the primary efficacy endpoint in Section 9.2. The Month 3 period will include pre-infusion and post-

infusion results at Week 10, pre-infusion and post-infusion results at Week 12, pre-infusion results at Week 14, and unscheduled pre-infusion assessments of sUA collected between Week 10 and Week 14 processed by the central laboratory. Section 9.1 shows the rules for inclusion of sUA values reported by local laboratories.

If the subject's proportion of hours is greater than or equal to 80% the subject will be called a responder for the Month 3 responder endpoint. Subjects meeting the stopping rule, i.e. has pre-infusion sUA values greater than 6 mg/dL at 2 consecutive scheduled visits (starting at Week 2) through Week 14 will be counted as non-responders. If only one sUA result is collected during Month 3 period, response will be based on the single value being less than 6 mg/dL. A subject with the proportion of hours, P, less than 80% will be counted as non-responders. Any other subject will be counted as a non-responder if sUA values are not collected during the Month 3 period.

The proportion of hours during the period where the sUA was less than 6 mg/dL will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). The number and proportion of subjects that discontinued treatment due to the stopping rule will be summarized. The number and proportion of responders will be summarized along with a 95% exact (Clopper-Pearson) CI for the proportion.

9.3.2. Proportion of Overall Responders Through Month 6

The proportion of overall responders through Month 6 is defined as subjects achieving and maintaining sUA < 6 mg/dL for at least 80% of the time during Months 3 and 6 combined. See Section 9.2 for the sUA results included in Month 6. See Section 9.3.1 for the sUA results included in Month 3. Section 9.1 shows the rules for inclusion of sUA values reported by local laboratories.

The definition of overall responders through Month 6 is dependent on the number of available sUA results available during Month 3 and during Month 6.

Case	Number of sUA Values at Month 3	Number of sUA Values at Month 6	Overall Response Determination
1	Any Number	0	Declared Overall Non-responder
2	0	Any Number	Declared Overall Non-responder
3	1	≥ 1 Record	If responder for both Month 3 and Month 6, then Declared Overall Responder If Non-responder for Month 3 and/or Month 6 then declared Overall Non-Responder
4	≥ 1 Record	1	If responder for both Month 3 and Month 6, then Declared Overall Responder If Non-responder for Month 3 and/or Month 6 then declared Overall Non-Responder

Case	Number of sUA Values at Month 3	Number of sUA Values at Month 6	Overall Response Determination
5	> 1 Record	> 1 Record	Overall Response is defined based on the weighted proportion of hours below the sUA < 6 mg/dL cutoff. See the remainder of this section.

Let T1 = the number of elapsed hours between the first and last non-missing sUA concentration among those collected between pre-infusion Week 10 and pre-infusion Week 14 collections.

Let T2 = the number of elapsed hours between the first and last non-missing sUA concentration among those collected between pre-infusion Week 20 and pre-infusion Week 24 collections.

Let W1 = the number of hours among the T1 hours where the sUA concentration was below 6 mg/dL.

Let W2 = the number of hours among the T2 hours where the sUA concentration was below 6 mg/dL.

The proportion of hours $P = 100 * \frac{W1+W2}{T1+T2}$
This is the weighted proportion of hours below 6 mg/dL.

If the subject's proportion of hours, P, is greater than or equal to 80% the subject will be called a responder for the overall responder endpoint. A subject with the proportion of hours, P, less than 80% will be counted as non-responders.

Subjects meeting the stopping rule, i.e. has pre-infusion sUA values greater than 6 mg/dL at 2 consecutive scheduled visits (starting at Week 2) through Week 24 will be counted as overall non-responders.

This endpoint will be analyzed for the ITT and mITT population. The mITT analysis will be considered the primary analysis for this endpoint.

The proportion of hours during the period where the sUA was less than 6 mg/dL will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). The number and proportion of subjects that discontinued treatment due to the stopping rule will be summarized. The number and proportion of responders will be summarized along with a 95% exact (Clopper-Pearson) CI for the proportion.

9.3.3. Proportion of Responders Achieving and Maintaining a sUA Below 5 mg/dL

The proportion of responders is defined as subjects achieving and maintaining sUA < 5 mg/dL for at least 80% of the time during Month 3, Month 6, and Overall (Months 3 and 6 combined). These will be calculated using the same method described for the primary efficacy endpoint (Section 9.2), and secondary endpoints reported in Sections 9.3.1 and Section 9.3.2. The endpoints will be analyzed using the same methodology described in Section 9.2, Section 9.3.1, and Section 9.3.2. This endpoint will be analyzed for the ITT and mITT population. The mITT analysis will be considered the primary analysis for this endpoint.

9.3.4. Change from Baseline in sUA

Observed values and change from MTX baseline at each scheduled time point, including pre-infusion and post-infusion results for sUA will be summarized for the mITT population using descriptive statistics (including n, mean, standard deviation, median, minimum, and maximum) based on observed values by pegloticase treatment status of the subject (On Treatment, Post-Treatment, and Overall). Subjects will only be summarized in the On Treatment visits for visits that occur (and results available) while still receiving pegloticase infusions. End of pegloticase infusion visit (windowed) if occurs, will also be considered On Treatment, as well as the Week 52 visit for subjects who complete treatment and study at Week 52. Post-Treatment visits are any post-baseline visits after the end of pegloticase infusions (or Week 52/EOS if subjects complete treatment). Overall status will include all visits for all subjects regardless of pegloticase treatment status. For the Overall status, sUA results at visits without an infusion will be summarized for the pre-infusion time point. See Section 9.1 for the description of inclusion of local laboratory results. The number and percentage of subjects at each visit with a sUA < 6 mg/dL will also be provided. The denominator will be the number of subjects in the population. A two-sided 95% normal-theory based CI will be presented for the mean observed value, mean change from MTX baseline, and mean change from MTX baseline for each visit. A similar analysis of change from pegloticase baseline based on observed values - will be presented for the mITT population.

An analysis of the observed values and change from MTX baseline at each scheduled time point will be completed for subjects who achieved the primary sUA responder endpoint vs. subjects who did not achieve the sUA response at Month 6 (see Section 9.2) will be produced using the mITT population.

Line plots of the observed mean pre-infusion sUA values at each scheduled visit will be presented using the mITT population. A graphical presentation of the mean pre-infusion sUA values by Month 6 sUA responders vs. non-responders, based on the primary endpoint definition of Month 6 response, will be produced for the mITT population.

By-subject plots of sUA values by time will be produced for the mITT population. Results from the central laboratory will be used. Section 9.1 shows the rules for inclusion of sUA values reported by local laboratories. Reference lines at 5 mg/dL and 6 mg/dL will be included.

9.4. Exploratory Efficacy Endpoints and Analyses

9.4.1. Proportion of Month 9 Responders

The proportion of Month 9 (Weeks 32, 34, 36) responders, will be defined as subjects achieving and maintaining sUA < 6 mg/dL for at least 80% of the time during Month 9.

This determination will be completed using the same linear interpolation method described for the primary efficacy endpoint in Section 9.2. The Month 9 period will include pre-infusion and post-infusion results at Week 32, pre-infusion and post-infusion results at Week 34, pre-infusion results at Week 36, and unscheduled pre-infusion assessments of sUA collected between Week 32 and Week 36 processed by the central laboratory. Section 9.1 shows the rules for inclusion of sUA values reported by local laboratories.

Subjects who completed the study at Week 24 (per Amendment 1 of the protocol) will be excluded from this analysis. For each subject on-study with participation per Amendment 2, if the subject's

proportion of hours is greater than or equal to 80% during Month 9, the subject will be called a responder for the Month 9 responder endpoint. Subjects meeting the stopping rule, i.e. has pre-infusion sUA values greater than 6 mg/dL at 2 consecutive scheduled visits (starting at Week 2) through Week 36 will be counted as non-responders. If only one sUA result is collected during Month 9 period, response will be based on the single value being less than 6 mg/dL. A subject with the proportion of hours, P, less than 80% will be counted as non-responders. Subjects who discontinued the study prior to Week 24 under Amendment 1 of the protocol will be considered non-responders. Any other subject will be counted as a non-responder if sUA values are not collected during the Month 9 period.

The proportion of hours during the period where the sUA was less than 6 mg/dL will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). The number and proportion of subjects that discontinued treatment due to the stopping rule will be summarized. The number and proportion of responders will be summarized along with a 95% exact (Clopper-Pearson) CI for the proportion.

9.4.2. Proportion of Month 12 Responders

The proportion of Month 12 (Weeks 48, 50, 52) responders, will be defined as subjects achieving and maintaining sUA < 6 mg/dL for at least 80% of the time during Month 9.

This determination will be completed using the same linear interpolation method described for the primary efficacy endpoint in Section 9.2. The Month 12 period will include pre-infusion and post-infusion results at Week 48, pre-infusion and post-infusion results at Week 50, pre-infusion results at Week 52, and unscheduled pre-infusion assessments of sUA collected between Week 48 and Week 52 processed by the central laboratory. Section 9.1 shows the rules for inclusion of sUA values reported by local laboratories.

Subjects who completed the study at Week 24 (per Amendment 1 of the protocol) will be excluded from this analysis. If the subject's proportion of hours is greater than or equal to 80% the subject will be called a responder for the Month 12 responder endpoint. Subjects meeting the stopping rule, i.e. has pre-infusion sUA values greater than 6 mg/dL at 2 consecutive scheduled visits (starting at Week 2) through Week 52 will be counted as non-responders. If only one sUA result is collected during Month 12 period, response will be based on the single value being < 6 mg/dL. A subject with the proportion of hours, P, less than 80% will be counted as non-responders. Subjects who discontinued the study prior to Week 24 under Amendment 1 of the protocol will be considered non-responders. Any other subject will be counted as a non-responder if sUA values are not collected during the Month 12 period.

The proportion of hours during the period where the sUA was less than 6 mg/dL will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). The number and proportion of subjects that discontinued treatment due to the stopping rule will be summarized. The number and proportion of responders will be summarized along with a 95% exact (Clopper-Pearson) CI for the proportion.
The proportion of Month 12 (Weeks 48, 50, 52) responders, defined as subjects achieving and maintaining sUA < 6 mg/dL for at least 80% of the time during Month 12.

9.4.3. Proportion of Month 9 5 mg/dL Responders

The proportion of responders, defined as subjects achieving and maintaining sUA < 5 mg/dL for at least 80% of the time during Month 9 will be calculated using the same method used for Month 9 Responders (6 mg/dL) (Section 9.4.1) will be used. The analysis will be completed for the ITT and mITT population.

9.4.4. Proportion of Month 12 5 mg/dL Responders

The proportion of responders, defined as subjects achieving and maintaining sUA < 5 mg/dL for at least 80% of the time during Month 12 will be calculated using the same method used for Month 12 Responders (6 mg/dL) (Section 9.4.2) will be used. The analysis will be completed for the ITT and mITT population.

9.4.5. Time to sUA > 6 mg/dL

The time to sUA > 6 mg/dL will be analyzed for the mITT population. The first pegloticase infusion date will be the reference date. Only the scheduled pre-infusion sUA values starting with Week 2 will be considered for determination of the endpoint. As was noted in Section 9.1, the local laboratory's value, may be used if the central laboratory's value at the scheduled time point is unavailable. The days until the sUA > 6 mg/dL will be calculated as:

EVTDAYS = EVNTDATE – REFDATE + 1, where EVNTDATE is the date of the earliest post-reference date where the pre-infusion sUA value (from either the local lab or central lab) is > 6 mg/dL. For subjects who do not have any sUA values > 6 mg/dL, their EVNTDATE will be censored at the latest collected sample with non-missing sUA result through Week 52. Kaplan-Meier (KM) estimates of the time to event will be reported along with a 95% CI for the median time. The time to event will also be presented graphically using a KM curve.

9.4.6. Time to two consecutive sUAs > 6 mg/dL

The time to two consecutive sUA > 6 mg/dL (starting at week 2) will be analyzed for the mITT population. The first pegloticase infusion date will be the reference date. Only the scheduled pre-infusion sUA values from the central laboratory starting with Week 2 will be considered for determination of the endpoint. As was noted in Section 9.1, the local laboratory's value, may be used if the central laboratory's value is unavailable. The days until the sUA > 6 mg/dL will be calculated as:

EVTDAYS = EVNTDATE – REFDATE + 1, where EVNTDATE is the date of the first of the two consecutive post-reference dates where the pre-infusion sUA value (from either the local lab or central lab) was > 6 mg/dL. Subjects with only a single elevated pre-infusion sUA and no subsequent sUA results available will be considered to have the event. Otherwise, for subjects who did not have two consecutive sUA values > 6 mg/dL, their EVNTDATE will be censored at the latest collected sample with non-missing sUA result through Week 52. KM estimates of the time to event will be reported along with a 95% CI for the median time. The time to event will also be presented graphically using a KM curve.

9.4.7. Peripheral Joint Urate Deposition Volume and Bone Erosion Score using DECT

For subjects from sites with the capabilities to determine joint urate deposition volume and bone erosion using DECT, the total urate volume is scheduled for collection at Day 1 of the Pegloticase + IMM Period, Week 24, Week 36, at the End of Pegloticase Infusion Visits (if applicable), and Week 52/End of Study/Early Termination Visit. Subjects who end pegloticase infusions prior to Week 52 should follow the scheduled timepoints but avoid a repeat DECT scan within 6 weeks of a prior scan. The analysis of DECT endpoints will be completed using the mITT population.

If there are 3 or more subjects who have an assessment of joint urate deposition volume, the observed values and the change from Day 1 in the total urate volume at each scheduled visit will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). Similarly, if 3 or more subjects have an assessment of bone erosion, the observed values and the change from Day 1 in the total bone erosion at each scheduled visit will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum).

9.4.8. Joints Affected by Tophi

The number of joints affected by tophi (via tophi assessment eCRF) are scheduled to be assessed at Screening, Week 24, Week 36, End of Pegloticase Infusions visit (if applicable), Week 52/End of Study/Early Termination Visit, Post-treatment Follow-up Month 3, and Post-treatment Follow-up Month 6. Using the mITT population, observed values and change from screening in the number of joints affected by tophi at each scheduled visit will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). If a subject has no joints affected by tophi, 0 will be used for number of joints affected.

9.4.9. Change from Baseline in Tender/Swollen Joints

Tender and swollen (excludes hip) joint counts will be recorded at the Week -4 (prior to the first dose of MTX) Visit during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks14, 24 and 36 Visits during the Pegloticase + IMM Period; and at the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of Study/Early Termination Visit, Post Treatment Follow-up Month 3, and Post-treatment Follow-up Month 6.

Tender and swollen joint counts will be assessed using the rheumatoid arthritis 66-68 joints.

Observed values, change from MTX baseline, and change from pegloticase baseline in the tender and swollen joint counts at each scheduled time point will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). A 95% normal-theory based CI for the changes from baseline will be presented. These analyses will be provided for the mITT populations.

9.4.10. Change from Baseline in HAQ-DI, HAQ Pain, and HAQ Health

The HAQ will be administered at the Screening and Week -4 (prior to the first dose of MTX) Visits during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if

applicable), the Week 52/End of Study/Early Termination Visit, Post Treatment Follow-up Month 3, and Post-treatment Follow-up Month 6.

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

The HAQ Pain question asks, "How much pain have you had in the past week?" on a scale of 0-100 where 0 represents no pain and 100 represents severe pain.

The HAQ Health question asks "Please rate how well you are doing on a scale of 0 to 100 (0 represents 'very well' and 100 represents 'very poor' health)".

Observed values and change from MTX baseline, and change from pegloticase baseline in the HAQ-DI, HAQ-Pain, and HAQ-Health score at each scheduled time point will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). A two-sided 95% normal-theory based CI for the changes from baseline will be presented. These analyses will be completed for the mITT population.

9.4.11. Change from Baseline in Patient Global Assessment of Gout

The patient global assessment will be collected at the Screening and Week -4 (prior to the first dose of MTX) Visits during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if applicable); the Week 52/End of Study/Early Termination Visit, Post Treatment Follow-up Month 3, and Post-treatment Follow-up Month 6. Subjects will respond to the statement, "Considering all the ways that gout affects you, circle the number below that best represents how your gout has affected you over the last week" using a numeric rating scale ranging from 0 (excellent) to 10 (very poor)

Observed values, change from MTX baseline, and change from pegloticase baseline in the patient global assessment at each scheduled time point will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). A 95% normal-theory based CI for the changes from baseline will be presented. The analysis will be completed for mITT population.

9.4.12. Change from Baseline in Physician Global Assessment of Gout

The physician global assessment will be collected at the Screening and Week -4 (prior to the first dose of MTX) Visits during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if applicable), the Week 52/End of Study/Early Termination Visit, Post Treatment Follow-up Month 3, and Post-treatment Follow-up Month 6. The same analyses described for the patient global assessment of gout (Section 9.4.11) will be used for the analysis of this variable. The analysis will be completed for the mITT population.

9.4.13. Change from Baseline in Subject Assessment of Average Pain, Least Pain, and Worst Pain

Joint pain will be assessed at the Screening and Week -4 (prior to the first dose of MTX) Visits during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if applicable); the Week 52/End of Study/Early Termination Visit, Post Treatment Follow-up Month 3, and Post-treatment Follow-up Month 6.

Subjects rate their average pain, least pain and worst pain over the past week on a scale from 0 to 10 with 0 = No joint pain and 10 = Worst Possible Joint Pain. The same analyses described for the patient global assessment of gout will be used for the analysis of these variables. These analyses will be completed for the mITT population.

9.4.14. Gout Chronic Response

Gout chronic response (GCR) criteria will be used to define subjects who achieve 20%, 50%, or 70% improvement in 3 of the 4 following measures at a scheduled time point:

- swollen joint count
- tender joint count
- HAQ health score
- HAQ pain score

Tender and swollen (excludes hip) joint counts will be recorded at the Week -4 (prior to the first dose of MTX) Visit during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks14, 24 and 36 Visits during the Pegloticase + IMM Period; and at the End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination Visit, Post Treatment Follow-up Month 3, and Post-treatment Follow-up Month 6. The HAQ will be administered at the Screening and Week -4 (prior to the first dose of MTX) Visits during the MTX Run-in Period; prior to pegloticase infusion at the Day 1 and Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if applicable), the Week 52/End of Study/Early Termination Visit, Post Treatment Follow-up Month 3, and Post-treatment Follow-up Month 6.

The GCR response will be determined at Day 1, Week 14, Week 24, Week 36, End of Pegloticase Infusion Visits, Week 52/End of Study/Early Termination Visit, Post Treatment Follow-up Month 3, and Post-treatment Follow-up Month 6.

A subject will be defined as a GCR20 (GCR50, GCR70) responder at a post-baseline assessment if they have at least a 20% (50%, 70%) reduction from the MTX baseline in 3 or more of the measures noted above. If a subject has 3 of the 4 measures and all 3 meet the reduction goal, the subject will be a responder.

In the other cases, including subjects with fewer than 4 of the criterion completed at the scheduled assessment, and subjects with all 4 criteria completed at the scheduled assessment who do not meet the 20% (50%, 70%) reduction criteria, subjects will be declared non-responders at the scheduled assessment.

Subjects who completed the study at Week 24 (per Amendment 1 of the protocol) will be excluded from Week 36, Week 52, and 3 and 6 month follow-up analyses.

This analysis will be performed for both the MTX and pegloticase baselines for the mITT population.

GCR20, GCR50, and GCR70 responses, and the number/percentage of subjects who achieved a 20%, 50%, and 70% reduction in each component endpoint in the GCR response, will be summarized. The percentage of GCR20, GCR50, and GCR70 responders will be calculated using the number of subjects in the population but excluding subjects who completed the study at Week 24 (per Amendment 1 of the protocol). A 95% Clopper-Pearson confidence interval will be for the percentage of GCR20, GCR50, and GCR70 responses. The mITT population will be used for these analyses.

9.5. Other Efficacy Endpoints and Analyses

9.5.1. Investigator Assessment of Clinical Status

At the Week 24, End of Pegloticase Infusion Visit (if last infusion occurred earlier than Week 50), and Week 52 / Early Termination visit, the investigator will assess the following items related to gout:

- Current clinical status
  - Presence of tophi
  - Notable tophi characteristics
- Gout flares occurring at a frequency of 2 or more per year (yes/no)
  - Number of flares occurring in the past 6 months
- Presence of chronically swollen joints due to gout (yes/no)
- Presence of chronic joint pain attributed to gout (yes/no)
- Symptoms the patient is specifically seeking to improve (yes/no)
  - Tophi presence/ size
  - Physical function due to tophi
  - Frequency of flares
  - Chronic joint swelling attributed to gout
  - Chronic joint pain attributed to gout
  - Other symptoms

This assessment was added as part of Protocol Amendment 2 and may not have data available for all subjects. The questions will be summarized descriptively by visit. The summarization of clinical status will be summarized using the mITT population.

10. Analysis of Pharmacokinetics and Anti-Drug Antibodies

For all subjects, serum samples for PK analysis will be collected prior to pegloticase infusion and after the end of infusion (prior to discharge) on Day 1 and at the Weeks 2, 4, 6, 8 and 36 Visits and prior to pegloticase infusion only at the Weeks 10, 14, 18, 22, 24; at the End of Pegloticase Infusions Visit (if applicable); and Week 52/End-of-Study/Early Termination Visit. Visits for frequent sampling of a subset of subjects who consent for additional non-infusion visit PK sampling (random, morning preferred) will occur at Week 1 and Week 7.

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 and maximum) for the PK Population

Concentrations below the limit of quantification (BLQ) collected on Day 1 pre-dose will be summarized as zero. All other concentrations BLQ will be excluded from the analysis summaries.

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. A by subject plot of total PG1-5, and individual 5 MTX polyglutamate values over time will be provided with Month 6 sUA Responders and Month 6 sUA Non-responders identified in the mITT population. A spaghetti plot of individual subjects for total PG1-5, PG1-2, PG3, PG3-5 will be provided with Month 6 sUA Responders and Month 6 sUA Non-responders identified in the mITT population. The percentage of total PG1-5 for PG1, PG2, PG3, and PG4-5 over time for all subjects in mITT population as well as Month 6 sUA Responders and Month 6 sUA Non-responders will be plotted in a bar graph. A listing of MTX polyglutamate concentrations will be provided, showing the subject, week/time point, collection date and time along with study day relative to first MTX treatment date, and the 5 MTX polyglutamate values and total MTX polyglutamate values.

Immunogenicity of pegloticase will be assessed via serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies. Samples will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 2, 4, 6, 8, 10, 14, 18, 22, 24, 36, at the End of Pegloticase Infusions Visit (if applicable); and 52/End of Study/Early Termination Visits and Post Treatment 3 month Follow-up Visit. Visits for frequent sampling of a subset of subjects who consent for additional non-infusion visit PK sampling will occur at Weeks 1 and 7. In the event of an AE suspected to be an infusion reaction, a serum sample for immunogenicity will be collected at that time or at the subsequent visit.

Using the mITT Population for anti-PEG IgG antibodies, the number and percentage of subjects with ADA positive at baseline, ADA positive at post-baseline but negative at baseline or with increase in titer from baseline, ADA positive at post-baseline but negative at baseline, and ADA with increase in titer from baseline, will be summarized by scheduled timepoint. Similarly for anti-uricase IgG antibodies, the number and percentage of subjects with ADA positive at baseline and post-baseline will be summarized by scheduled timepoint.

Kaplan-Meier estimates of the time to positive anti-PEG response, 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.

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) and ADA negative (defined as negative for both anti-PEG and anti-uricase antibodies) for each visit. This analysis will be provided for the mITT Population.

11. Safety

Safety analyses will be based on the ITT population and the MITT population, as appropriate.

Safety will be assessed via AEs, concomitant medication use monitoring (refer to Section 8.3), physical examinations, vital signs, clinical safety laboratory evaluations (complete blood count, chemistry, urine uric acid: creatinine ratio), pregnancy testing (if applicable), electrocardiograms (ECGs), and AEs of special interest (i.e., infusion reactions (IRs), anaphylaxis, gout flares, and cardiovascular events).

All safety information will be provided in subject listings.

11.1. Extent of Exposure

Study drug exposure will be summarized using the duration of treatment (in days), number of doses, and total dosage received for MTX and pegloticase. The usage of prophylaxis treatments (folic acid, IR usage of fexofenadine in the evening prior to pegloticase infusion, IR prophylaxis of fexofenadine, acetaminophen, methylpredisone, and hydrocortisone on the morning prior to pegloticase infusion) will be provided in listings only. Interruptions in pegloticase infusions will be summarized. Reasons for infusion interruptions will be provided in the listings.

For the MTX Run-in Period, the following will be summarized:

- Duration of treatment defined as the last dose of MTX prior to the Day 1 visit date – first dose date of MTX + 1 (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)
- Total MTX dosage 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 MTX dose (in mg) (total dosage for the MTX Run-in Period divided by number of doses taken during the MTX Run-in Period) (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 + IMM Period, the following will be summarized:

- Pegloticase
    - Number of pegloticase infusions received overall (summarized with frequency summary along with descriptive statistics of mean, SD, median, minimum, and maximum)
    - Duration in days between first and last pegloticase infusion, defined as last infusion date – first infusion date + 1 (summarized with descriptive statistics of mean, SD, median, minimum and maximum)
    - Number of incomplete infusions received (summarized with frequency summary along with descriptive statistics of mean, SD, median, minimum and maximum)
    - Number of interrupted infusions

  - summarized with frequency summary along with descriptive statistics of mean, SD, median, minimum and maximum)
- At each scheduled Pegloticase infusion visit
  - 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
  - Duration of MTX dosing during the Pegloticase + IMM Period, defined as the last MTX date – first MTX dosing date (on or after the date of the Day 1 visit) + 1
  - Cumulative MTX dosage (in mg) received during the Pegloticase + IMM period
  - Average MTX dose (in mg) (total dosage for the Pegloticase + IMM Period divided by number of doses taken during the Pegloticase + IMM Period) (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:

- MTX
  - Duration of MTX dosing, defined as the last MTX date – first MTX dosing date (on or after the date of the Day 1 visit) + 1
  - Cumulative MTX dosage (in mg) received
  - Number of subjects with MTX dosage reductions from planned 15 mg/week.
  - Total MTX dosage (in mg) per dose overall

11.2. Treatment Compliance

Other than the summarizations of Pegloticase infusions described in Section 11.1, the compliance with Pegloticase will not be summarized.

Other than the summarizations of MTX exposure, the compliance with MTX will not be summarized.

11.3. Adverse Events

All adverse events will be coded using MedDRA version 20.1. AE monitoring will begin from the signature of the ICF until the 6 month Post Treatment Follow-up Visit. SAE monitoring will begin from the signature of the ICF until the 6 month Post Treatment Follow-up Visit.

Adverse events with an onset date strictly prior to the first MTX treatment in the MTX Run-in Period will be called non-treatment-emergent events.

Treatment-emergent AEs (TEAEs) for the MTX Run-In period are defined as events with an onset date on or after the first dose of MTX (but not on or after the first infusion date of pegloticase in subjects who entered the Pegloticase + IMM Period) through 30 days after the last dose of MTX for subjects who did not receive pegloticase.

TEAEs for the Pegloticase + IMM Period are defined as events that occur on or after the start date of the first pegloticase infusion through 30 days after the last dose of pegloticase and/or MTX (whichever is later).

Adverse events with an onset date more than 30 days after the last dose of pegloticase and/or MTX (whichever is later), will be adverse events in the follow-up period.

All AEs, both serious and non-serious, will be assessed for severity using the Rheumatology Common Toxicity Criteria (CTC) v2.0. Missing data conventions for AEs are described in Section 6.3.2. The imputed onset dates will be used to determine the period of onset. Summaries of TEAEs in the MTX Run-in Period will be provided using the ITT and mITT populations. Summaries of TEAEs in the Pegloticase + IMM Period will be summaries for the mITT population.

An overall summary of TEAEs will be provided by for the MTX Run-in Period and Pegloticase + IMM 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
- TEAEs Related to pegloticase (applicable to Pegloticase + IMM Period only)
- Serious TEAEs Related to MTX
- Serious TEAEs Related to pegloticase (applicable to Pegloticase + IMM Period only)
- TEAEs with an Rheumatology CTC Criteria of 3 or higher
- TEAEs leading to permanent withdrawal of MTX
- TEAEs leading to permanent withdrawal of pegloticase (applicable to Pegloticase + IMM Period only)
- TEAEs Related to MTX leading to permanent withdrawal of MTX
- TEAEs Related to pegloticase leading to permanent withdrawal of pegloticase (applicable to Pegloticase + IMM Period only)
- TEAEs leading to study discontinuation
- TEAEs Related to MTX leading to study discontinuation
- TEAEs Related to pegloticase leading to study discontinuation (applicable to Pegloticase + IMM Period only)

- TEAEs leading to death

Using the mITT population, an overall summary of AEs occurring during the follow-up period (with onset more than 30 days after the last dose of study medication), 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 an Rheumatology CTC Criteria of 3 or higher
- AEs leading to study discontinuation
- AEs leading to death

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

Additional AE summaries will be provided by onset period, including the number, percentage of subjects, experiencing TEAEs for the following:

- TEAEs overall and by SOC and PT for the: MTX Run-in Period, Pegloticase + IMM Period, and Follow-up Period
- TEAEs by maximum severity, overall and by SOC and PT for the: MTX Run-in Period and Pegloticase + IMM Period
- TEAEs related to MTX overall and by SOC and PT for the: MTX Run-in Period and Pegloticase + IMM Period
- TEAEs related to pegloticase overall and by SOC and PT for the Pegloticase + IMM Period only
- TEAEs Related to MTX by maximum severity, overall and by SOC and PT for the: MTX Run-in Period and Pegloticase + IMM Period.
- TEAEs Related to Pegloticase by maximum severity, overall and by SOC and PT for the Pegloticase + IMM Period only
- Serious TEAEs, overall and by SOC and PT for the: MTX Run-in Period, Pegloticase + IMM Period, and Follow-up Period
- TEAEs leading to permanent withdrawal of MTX, overall and by SOC and PT for the: MTX Run-in Period, and Pegloticase + IMM Period)
- TEAEs leading to permanent withdrawal of pegloticase, overall and by SOC and PT for the Pegloticase + IMM Period only

The incidence per person years of exposure to MTX, and incidence per person years of exposure to pegloticase will be provided on all tables except those summarizing events by maximum intensity, and those for the post-treatment follow-up period. For summaries by SOC, PT, and maximum severity, a subject will only be counted once 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. For summaries by SOC and PT only, a subject will be counted at most once 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.

In addition to the listing of all AEs, separate listings will be provided for serious AEs, AEs leading to withdrawal of MTX, AEs leading to withdrawal of pegloticase, AEs leading to study discontinuation, AEs of special interest, and AEs leading to death. TEAEs and the period of onset will be identified on each listing.

11.3.1. Adverse Events of Special Interest

Adverse events of special interest will include: infusion reactions (IRs), anaphylaxis, gout flares, and cardiovascular events:

IRs and Anaphylaxis

IRs and anaphylaxis reactions are defined in the protocol (see Protocol section 9.5.4.1.1.5). These events are identified by the investigator on the eCRF. The signs and symptoms associated with each event are entered on the eCRF and will be coded to the MedDRA dictionary. IRs and anaphylaxis events, and the associated signs and symptoms, will be summarized by SOC, PT, severity, and the time relative to the most recent pegloticase infusion. Time relative to the most recent pegloticase infusion will be categorized as: day of infusion, 1-2 days after infusion, and > 2 days after infusion. Summaries of IRs and anaphylaxis will be tabulated only if 5 or more subjects with either IR or anaphylaxis occur.

Cardiovascular Events

Cardiovascular events will include Major Adverse Cardiovascular Events (MACE).

Any MACE including Non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure. The following search algorithm will be used to identify possible MACE:

- For cardiovascular death: Standardized MedDRA Queries (SMQ): Myocardial infarction (broad), Haemorrhagic central nervous system vascular conditions (narrow), Ischaemic Central Nervous System (CNS) 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 circulatory or cardiac conditions (excl torsades de pointes) (broad), Torsade de pointes/QT prolongation (broad), 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)

Cardiovascular events will be tabulated only if 5 or more subjects have experienced a cardiovascular event. Using the ITT and mITT population, cardiovascular events will be summarized by MedDRA SOC and PT for the MTX Run-in Period. Using the mITT population, cardiovascular events will be Pegloticase + IMM Period.

Gout Flares

The number and percentage of subjects who experienced a gout flare (recorded in the AE eCRF), and number of gout flare per subject will be summarized for the MTX Run-in Period using the ITT population. Percentages will be calculated using the number of subjects in the ITT population. The number and percentage of subjects who experienced a gout flare and number of gout flares per subject during the pegloticase + IMM Period (recorded in the AE eCRF) will be provided for the mITT population. These events will be further summarized as occurring from the period from Day 1 to Week 12, after Week 12 – Week 24, after Week 24 – Week 36, and after Week 36 – Week 52, and after Week 52. For the full pegloticase + IMM period, percentages will be calculated using the number of subjects in the mITT population. Events are summarized for each period according to the onset date of the flare, and only summarized in the period of onset. For the Day 1 to Week 12, percentages will be based on the number of subjects in the mITT population. In addition, these events during the pegloticase + IMM period will be further summarized by month of occurrence, e.g., Month 1, Month 2, up to Month 12. One month is defined as 30 days. For the other time periods of the pegloticase + IMM period, percentages will be based on the number of subjects who had follow-up at least as far as the start of the period-specific time period. The 30 days following the end of treatment are included in the follow-up time period.

At the assessments Week -4, Week -2, Day 1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week14, Week 16, Week 18, Week 20, Week 22, Week 24, Week 26, Week 28, Week 30, Week 32, Week 34, Week 36, Week 38, Week 40, Week 42, Week 44, Week 46, Week 48, Week 50, Week 52/End of Study/Early Termination, Month 3 and Month 6 Follow-up, assessments of gout flares are collected on a gout flare assessment eCRF. Using the ITT and mITT population, the incidence of gout flares is assessed. If the subject has experienced a gout flare, the incidence of pain different than normal, incidence of pain at rest greater than 3 on a scale from 0-10, incidence of swelling in joints, and intensity of the flares (on a scale of 0-10) are assessed. All questions except the intensity of flares will be summarized using number and

percentage of responses. Percentages will be based on the number of subjects assessed at the visit. The intensity of flares will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be summarized.

11.4. Laboratory Evaluations

Blood (for hematology and clinical chemistry) and urine (for uric acid: creatinine ratio) samples will be collected at the Screening, Week -4 (prior to the first dose of MTX), and Week -2 Visits during the Screening/MTX Run-in Period; prior to pegloticase infusion on Day 1 and at the Weeks 2, 6, 14, 22, 24 and 36 Visits during the Pegloticase + IMM Period; and the End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination, and 3 and 6 month Post Treatment Follow-up Visits.

Safety laboratory assessments will include:

- Hematology: complete blood count with differential (hemoglobin concentration, hematocrit, erythrocyte count, platelet count, leukocyte count, and differential leukocyte count)
- Chemistry: transaminases (aspartate aminotransferase, alanine aminotransferase), alkaline phosphatase, total bilirubin, creatinine, glucose, sodium, potassium, calcium, chloride, total protein, blood urea nitrogen, and human chorionic gonadotropin (at the Screening Visit for all female subjects of childbearing potential)
- Urine: uric acid: creatinine ratio and human chorionic gonadotropin (at all visits except the Screening Visit for all female subjects of childbearing potential)

A central study laboratory will be used for all protocol-specified clinical laboratory parameters.

Laboratory results will be displayed using the conventional units. for all summaries and listings. Clinical laboratory test results (hematology, chemistry, and urinalysis) and their changes from MTX baseline will be summarized by visit for the ITT and mITT population using descriptive statistics.

If a continuous laboratory value is reported as either below or above the limits of quantification, the qualifiers will be dropped and the numeric value used in the analysis (e.g., "< 3" will be summarized as "3" and "> 200" will be summarized as "200").

For all laboratory tests, results will be categorized as low, normal, or high based on their normal ranges. Results out of range will be identified as such on subject listings.

Using the ITT and mITT populations, shift tables using categories of low, normal, and high, comparing laboratory test results from MTX baseline to each visit will be presented with percentages based on subjects with a non-missing value at baseline and post-baseline visit. A summary of elevated liver function test values as well as Hy's law will be provided by visit and for any post-baseline visit for the ITT and mITT populations:

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

For tests where the Common Terminology Criteria for Adverse Events (CTCAE) criteria is available, shift tables will be based on the CTCAE grade. The CTCAE version 4.03 will be used for these summaries.

11.5. Pregnancy Tests

Pregnancy test results will be provided in a listing.

11.6. Vital Signs

Routine vital signs, including blood pressure, respiratory rate, temperature, and heart rate will be measured at Screening, Week -4 and at all infusion visits during the Pegloticase + IMM Period and the End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and 3 and 6 month Post Treatment Follow-up Visits. During the Pegloticase + IMM Period study visits, vitals should be taken before the pegloticase infusion and any time after the end of the infusion, but prior to subject's discharge/release from the site. In addition, if immediate infusion-associated events are noted during the infusion, vital signs will be monitored at least every 30 minutes until resolution or stabilization of the AE.

Weight will be summarized in kilograms. Weight and BSA is recorded at the Screening Visit; prior to pegloticase infusion on Day 1 and at the Weeks 8, 16, 24, 36, and at the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and Months 3 and 6 Post Treatment Follow-up Visits.

Height will be collected at the Screening Visit only. Height is recorded in units of centimeters (cm). Body Mass Index (BMI) will be determined using the weight recorded in kg and the height measured at screening.

Descriptive summaries of observed and change from MTX baseline values will be presented for each vital sign parameter by visit, using the ITT and mITT populations. 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.

The following conversion factor will be used to convert any temperatures reported in degrees Fahrenheit to Celsius:

Temperature (in °C) = 5/9 (Temperature [in °F]-32).

The following conversion factor will be used to convert any weights reported in pounds to kilograms:

Weight [kg] = Weight [in lbs] * 0.4536.

The following formula will be used to determine the BMI (in kg/m^2) using weight [in kg] and height [in cm]:

BMI = Weight / ((Height/100) * (Height/100));

11.7. Electrocardiograms

An electrocardiogram (ECG) will be performed on Day 1 before the first Pegloticase infusion for all subjects and at the discretion of the Investigator thereafter. The results will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated as clinically significant (CS) or not clinically significant (NCS) by the investigator.

Using the mITT population, a summary will be provided of subjects at Day 1 (using the count and percentage of subjects) with:

- Normal
- Abnormal NCS
- Abnormal CS

Percentages will be based on the number of subjects with an assessment completed.

Because the post-Day 1 ECGs are done at the discretion of the investigators, only the following summaries will be provided using the mITT population:

- Incidence of post-Day 1 Abnormal ECGs (includes NCS and CS) findings
- Incidence of post-Day 1 Abnormal, Clinically Significant ECGs

For the post-Day 1 ECG summary, percentages will be calculated using the number of subjects in the MITT population.

11.8. Physical Examination

A complete physical examination will be performed at the Screening Visit and will include assessments for presence of tophi, as well as gout history and symptom severity. A targeted physical examination per the investigator judgement but at a minimum should include heart, lungs and abdominal exam and include a joint and skin evaluation and assessment of AEs at Week 4, Day 1, and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20, 24, 36, the End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination, and 3 and 6

month Post Treatment Follow-up Visits.

Physical examination data will be listed. No summarizations of the physical examination data will be presented.

12. Changes from Analysis Planned in Protocol

For the summary of sUA, the number and percentage of subjects with a value < 6 mg/dL at each visit was added.

The exploratory endpoint of time to first sUA > 6 mg/dL in subjects receiving pegloticase with MTX was adjusted to time to the first pre-infusion sUA > 6 mg/dL in subjects receiving pegloticase with MTX.

The exploratory endpoint of time to two consecutive sUA > 6 mg/dL (stopping rule) in subjects receiving pegloticase with MTX was adjusted to time to two consecutive pre-infusion sUA > 6 mg/dl (stopping rule) in subjects receiving pegloticase with MTX.

The summary of investigator assessment of clinical status was added, based on the addition of a new eCRF collecting this information.

13. Programming Considerations

13.1. General Considerations

- All TLFs will be produced in landscape format.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color)
- Specialized text styles, such as bolding, italics, borders, and shading will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., m^2, C_{trough}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.
-

13.2. Table, Listing, and Figure Format

13.2.1. General

- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:

Horizon Therapeutics Ireland DAC

Protocol HZNP-KRY-201

- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

- Each Table, Figure, and Listing is identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Population)

13.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the population columns. Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

13.2.5. Body of the Data Display

13.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;

- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

13.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
SD	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have

an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the SOC (or treatment class) sorted alphabetically. Within the body system, drug class and SOC, medical history (by preferred term), drug term (by preferred name, and adverse events (by preferred term) are displayed alphabetically.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of the populations the subject was treated in (ITT only, ITT and mITT population, Not Treated, Screen Failure) subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as "UN" for missing days and "UNK" for missing months (e.g. UNJUL2000, UNUNK2000). Dates that are missing because they are not applicable for the subject are output as "NA", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available

13.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in [redacted] and [redacted] describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

15. Index of Tables

Table Number	Name	Analysis Sets
[redacted]	[redacted]	[redacted]

Table Number	Name	Analysis Sets
[redacted]	[redacted]	[redacted]

Table Number	Name	Analysis Sets
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table Number	Name	Analysis Sets
[redacted]	[redacted]	[redacted]

16. Index of Figures

Figure Number	Name	Analysis Set(s)
[redacted]	[redacted]	[redacted]

17. Index of Listings

Listing Number	Name	Analysis Set (Example)
[redacted]	[redacted]	[redacted]

Listing Number	Name	Analysis Set (Example)
[redacted]	[redacted]	[redacted]

18. References

Karvanen J. The statistical basis of laboratory data normalization. Drug Information Journal. 2003; 37:101-107