Statistical Analysis Plan

Protocol Title:	A Phase 4, Randomized, Double-blind, Multicenter Non-inferiority Trial Evaluating the Efficacy and Safety of Intravenous KRYSTEXXA® (pegloticase) Administered Every 4 Weeks Compared with KRYSTEXXA Administered Every 2 Weeks with Co-administration of Weekly Doses of Methotrexate, Followed by an Open-label Extension, in Participants with Uncontrolled Refractory Gout (FORWARD II)
Short Protocol Title:	A trial to investigate the non-inferiority of pegloticase administered every 4 weeks (Q4W) with MTX compared with every 2 weeks (Q2W) with MTX in participants with uncontrolled refractory gout
Protocol Number:	HZNP-KRY-409
NCT Number:	NCT06229145
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SAP Date:	**Document Version** — **Date** Amendment # 1 (v2.0) — 09 May 2025 **Amendment # 2 (V3.0)** — **20 August 2025**

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	04 Oct. 2024	NA
Amendment 1	09 May 2025	Section 4.2: Added subgroups for race and sex

		Section 9.5.1.1 Added rationale for non-responder imputation as the primary method for handling missing data Section 9.5.2 Added sensitivity analysis for the secondary endpoint for handling Intercurrent Events (ICE) as done for the primary endpoint Section 9.6.2.1 Added exposure-adjusted incidence rate (EAIR) and 95% CI estimates for AE of special interest (AESI), and update Standard MedDRA Query (SMQ) to Adverse Medical Query (AMQ) per Amgen standard [redacted]
Amendment 2	**20 August 2025**	**Section 5 Added the EAIR and SAIR calculation methods.** **Section 9.6.2.1 Added analysis for study duration adjusted incidence rate (SAIR) for AESIs**

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List of Abbreviations

Abbreviation	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMQ	Adverse Medical Query
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
BAP	Biomarker analysis plan
BLQ	Below the limit of quantitation
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
CNS	Central nervous system
CPMS	Clinical pharmacology, modeling & simulation
CR	Complete response
CRF	Case report form
CTC	Common toxicity criteria
CTCAE	Common Toxicity Criteria for Adverse Events
DB	Double blind
DI	Disability index
DM	Data management
DMP	Data management plan
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	**End of study**
EOT	End of treatment
ET	Early termination
FAS	Full Analysis Set
FU	Follow-up

GSO	Global study operations
[redacted]	
HLGT	High level group term
ICE	Intercurrent event
IgG	Immunoglobulin G
IP	Investigational product
IPD	Important protocol deviation
IR	Infusion reaction
ISR	Injection site reaction
IV	Intravenous(ly)
LFT	Liver function test
LS	Least squares
MACE	Major adverse cardiovascular event(s)
MAS	MTX analysis set
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model for repeated measures
MR	Modified response
MTX	Methotrexate
OL	Open label
PD	Progressive disease
PEG	Polyethylene glycol
PK	Pharmacokinetics
PPAS	Per-protocol analysis set
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
Q1, Q3	First quartile, third quartile
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
QOL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SAIR	**Study duration Adjusted Incidence Rate**

SD	Stable disease
SE	Standard error
SMQ	Standard MedDRA query
SOC	System organ class
sUA	Serum uric acid
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TFLSD	TFL Shell Document
[redacted]	
ULT	Urate-lowering therapy
WHODD	World health organization drug dictionary

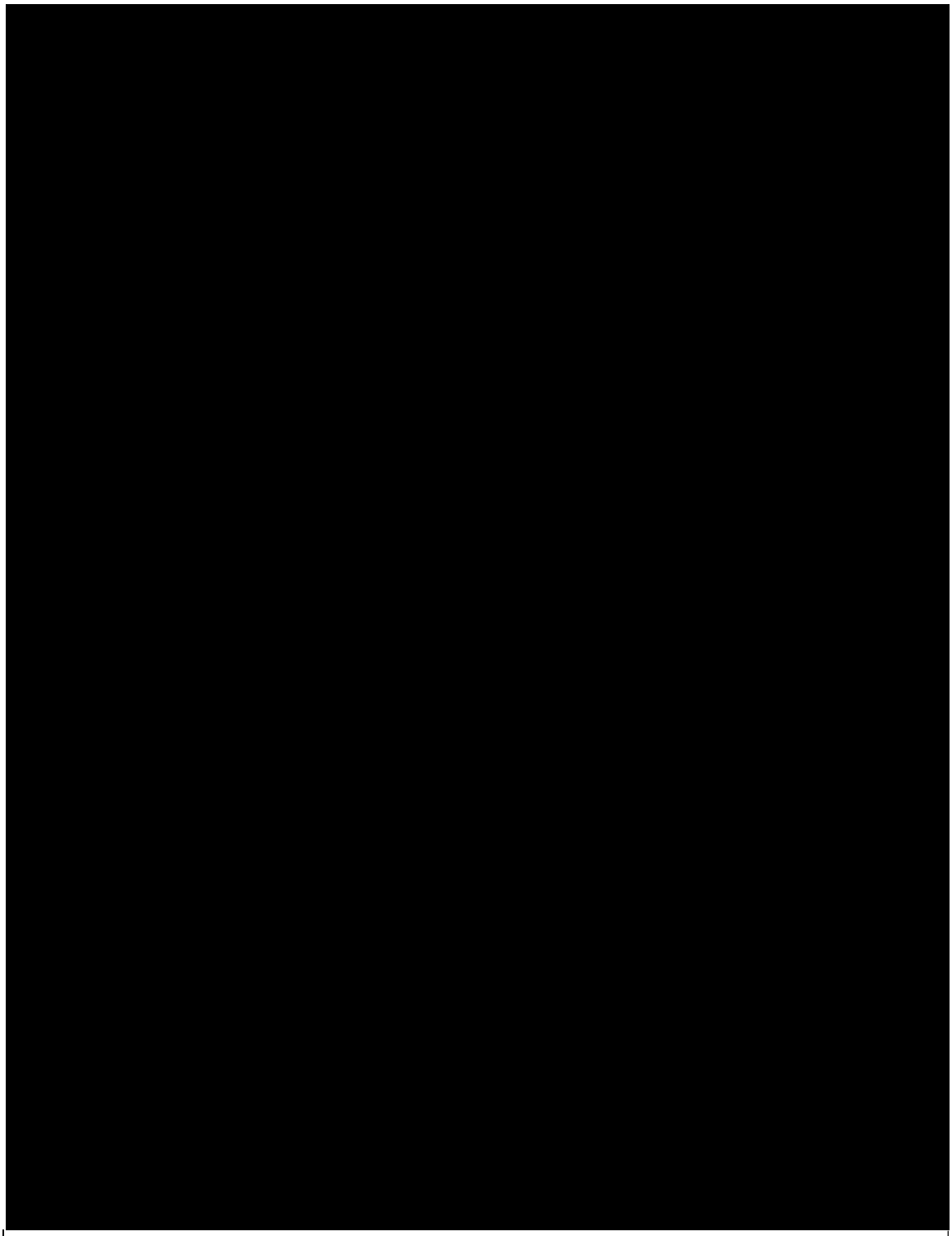
1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study HZNP-KRY-409, KRYSTEXXA, dated 6 March 2024. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints/Estimands and Hypotheses

2.1 Objectives and Endpoints/Estimands

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



PK and Immunogenicity	
• Assess the PK of pegloticase	• Serum concentrations of pegloticase
• Assess MTX polyglutamate concentrations	• MTX polyglutamate concentrations

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

Estimands for Primary Objectives

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

Component	Description
Population	Participants with uncontrolled refractory gout who are randomized and receive at least one dose of pegloticase 16 mg or 8 mg
Variable	Achieving response (sUA<6 mg/dL) during Month 6
ICE	Early discontinuation of pegloticase (regardless of subsequent initiation of urate lowering therapies); meeting sUA discontinuation criterion (sUA values > 6 mg/dL at 2 consecutive scheduled visits [excluding post-infusion sUA at infusion visits] starting at Week 2)
ICE Strategy	A composite strategy will be used in which participants who meet the sUA discontinuation criterion, or have only 1 sUA observation available during Month 6, or have no sUA during Month 6 are considered treatment failures (non responders). Available sUA

	results during Month 6 from participants who discontinue pegloticase for reasons other than meeting the sUA discontinuation criterion prior to Week 24 will be used in the response calculation.
Population-level Summary	Stratified difference in response rate between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX

Estimands for Secondary Objectives

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

Component	**Description**
Population	Participants with uncontrolled refractory gout with tophus (or tophi) present at Baseline who are randomized and receive at least one dose of pegloticase 16 mg or 8 mg
Variable	Achieving complete resolution of ≥ 1 tophus (using digital photography) at Week 24
ICE	Early discontinuation from pegloticase (regardless of subsequent initiation of urate lowering therapies)
ICE Strategy	Tophi data collected after a participant has discontinued from pegloticase will be included in analysis (treatment policy)
Population-level Summary	Difference in the proportion of participants with complete resolution of ≥ 1 tophus at Week 24 between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX

2.2 Hypotheses and/or Estimations

The primary objective is to demonstrate that pegloticase 16 mg Q4W (every 4 weeks) with methotrexate (MTX) is non-inferior to pegloticase 8 mg Q2W (every 2 weeks) with MTX in achieving sustained normalization of sUA < 6 mg/dL for at least 80% of the time during Month 6.

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

$H_{0:}\ \pi_c - \pi_t \geq 0.2$ vs $H_{A:}\ \pi_c - \pi_t < 0.2$,

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

π_c = proportion of responders during Month 6 for pegloticase 8 mg Q2W with MTX

- Null hypothesis (H_0): pegloticase 16 mg Q4W with MTX is inferior to pegloticase 8 mg Q2W with MTX in achieving the sustained normalization of sUA < 6 mg/dL for at least 80% of the time during Month 6 by 20% or more.
- Alternative hypothesis (H_A): pegloticase 16 mg Q4W with MTX is not inferior to pegloticase 8 mg Q2W with MTX in achieving the sustained normalization of sUA < 6 mg/dL for at least 80% of the time during Month 6 by 20% or more.

3. Study Overview

3.1 Study Design

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

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

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

Participants will continue to take MTX from Week -4 to Day 1 (the MTX Run-in Period). If a participant does not tolerate MTX 15 mg during the MTX Run-in Period, the participant will be considered a screen failure and will be discontinued from the trial.

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

During the double-blind Pegloticase + MTX Period, participants will receive IV infusions (pegloticase or placebo) Q2W in order to maintain the blind. During the open-label

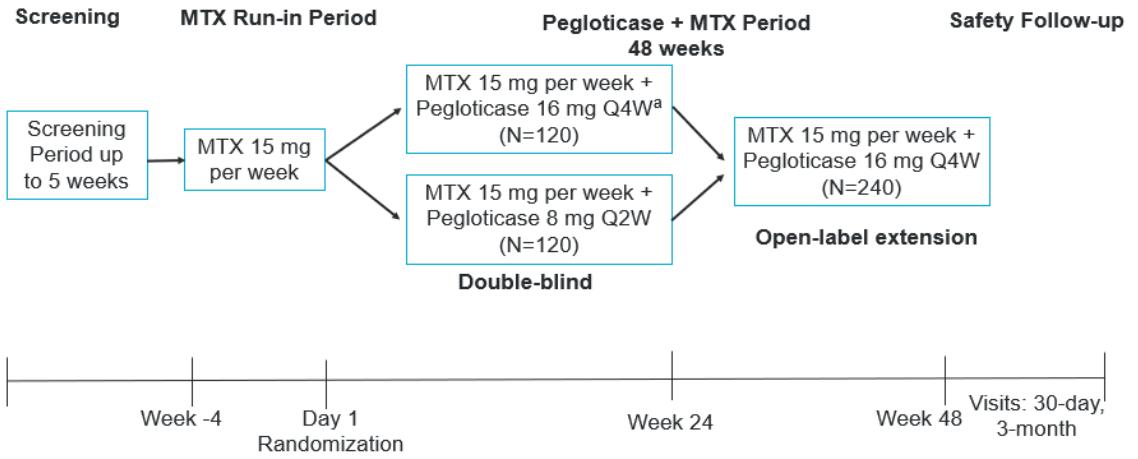
extension, all participants will receive pegloticase 16 mg administered IV (intravenous) Q4W from Week 24 through Week 44 Visit. Pegloticase and placebo for pegloticase will be administered after all pre-dose trial visit assessments have been completed at each visit. The sUA discontinuation criterion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

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

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

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

Figure 1. Study Design



MTX = methotrexate; Q2W = every 2 weeks; Q4W = every 4 weeks
[a]In order to maintain the blind during the double-blind portion of the trial, participants in the 16 mg Q4W treatment group will receive pegloticase 16 mg administered IV Q4W from Day 1 through the Week 20 Visit and placebo for pegloticase IV Q4W from Week 2 through Week 22.

3.2 Sample Size

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

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

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

3.3 Adaptive Design

Not Applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

The analysis of the responder endpoints and tophi resolution will be adjusted for the following covariates: presence of tophi (Yes, No) for responder endpoints only, age, baseline weight, baseline ADA status and baseline eGFR, as appropriate. The analyses of other endpoints will be adjusted for presence of tophi and age.

4.2 Subgroups

Analyses on the primary efficacy endpoint will be performed for the following subgroups.

- age (<50 and >= 50)
- weight (< median, >= median)
- race (white, non-white)
- sex (male, female)
- presence of tophi (Yes, No)
- baseline anti-PEG status (positive, negative)
- treatment-emergent anti-PEG status (positive, negative) [defined in Section 9.6.7]

5. Definitions

Enrollment: A participant is considered enrolled on study day 1 when the investigator confirms that the participant has met all eligibility criteria and is randomized.

Age at enrollment: Participant age at enrollment will be determined using the age in years reported in the clinical database.

Baseline: For analysis of laboratory parameters, baseline is defined as the last non-missing valid observation prior to the first dose of MTX during the MTX Run-in Period. For all other analyses, baseline is defined as the last non-missing valid observation prior to the first dose of pegloticase during the double blind (DB) treatment period. In cases where baseline measurements are taken on the same day as MTX or pegloticase during

the treatment period and no times are reported, it will be assumed that these measurements are taken prior to drug being administered. Missing baseline evaluations will not be imputed and will be considered missing.

Investigational Product: The term 'investigational product' is used in reference to both pegloticase, placebo for pegloticase and methotrexate.

sUA Discontinuation Criterion: Participants will be discontinued from pegloticase if sUA values are > 6 mg/dL at 2 consecutive scheduled visits (excluding post-infusion values at infusion visits) starting at Week 2.

sUA Alternative Discontinuation Criterion: In the real-world setting, some physicians may choose to discontinue pegloticase if participants have a single sUA value > 6 mg/dL (rather than 2 consecutive sUA values > 6 mg/dL) excluding post-infusion values at infusion visits, starting at Week 2.

Change from Baseline: Change from Baseline is the arithmetic difference between post-dose assessments and Baseline value.

Change from Baseline = (Post-baseline Value – Baseline Value)

Body Surface Area (BSA): BSA is calculated using Mosteller's formula as follows:

BSA= sqrt [Height(cm) x Weight(kg) / 3600]

Screening date: Screening date is defined as the date the informed consent was signed.

Treatment-emergent Adverse Event (TEAE): A TEAE is any adverse event starting on or after the first dose of investigational product and up to including 30 days after the last dose of investigational product.

Study Day 1: Study day 1 is defined as the first day of administration of the investigational product (relative to start date of pegloticase or MTX) during the double-blind treatment period. The day prior to study day 1 is considered as day -1.

Study Day: Two different study days will be calculated, the MTX Study Day and the Pegloticase Study Day. The MTX Study Day will be determined relative to the first dose of MTX during the MTX Run-in Period and will be defined as below.

- Before the 1st dose date: MTX Study Day = Date of assessment – the 1st dose date of MTX

- On or after the 1st dose date: MTX Study Day = Date of assessment – the 1st dose date of MTX + 1

The pegloticase Study Day will be determined relative to the first infusion of pegloticase where pegloticase study day will be defined as below.

- Before the 1st dose date: Pegloticase Study Day = Date of assessment – the 1st dose date of pegloticase
- On or after the 1st dose date: Pegloticase Study Day = Date of assessment – the 1st dose date of pegloticase + 1

End of Study: End of study for each participant is defined as the date when the participant completed the last protocol-specified procedure through Week 48 (or earlier if discontinued) and does not include the Month 3 Follow-up visit. The date will be recorded on the End of Study CRF (case report form) page. Participants are expected to complete the follow-up visits but are considered to have completed the study if they complete visits through Week 48.

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

Exposure Adjusted Incidence Rate (EAIR) While-on-treatment:

EAIR is calculated as the number of subjects with events divided by the sum across all participants of either time to first event or treatment exposure time (in years) if no event occurs within the specified period

Study duration Adjusted Incidence Rate (SAIR) While-on-study:

SAIR is calculated as the number of subjects with events divided by the sum across all participants of either time to first event or time on study (in years) if no event occurs within the specified period.

6. Analysis Sets

For the efficacy analyses, participants will be analysed according to the randomized treatment; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received. In the event a participant receives more than one treatment, the participant will be summarized by the treatment received most frequently.

6.1 Full Analysis Set

The Full Analysis Set (FAS) includes all participants who receive at least 1 dose of pegloticase. For the Open Label (OL) Pegloticase + MTX Period, only participants in the FAS during the Double Blind (DB) Pegloticase + MTX Period who enter the OL period (i.e. receive at least one dose of pegloticase 16 mg in OL Period) will be included in the analyses. The FAS will be used to analyze endpoints related to the efficacy objectives.

6.1.1 Primary Analysis Set

Not applicable.

6.2 Safety Analysis Set

The Safety Analysis Set includes all participants who receive at least 1 dose of pegloticase. For the OL Pegloticase + MTX Period, only participants in the Safety Analysis Set during DB Pegloticase + MTX Period who enter the OL Period (i.e. receive at least one dose of pegloticase 16 mg in the OL Period) will be included in the analyses.

This analysis set will be used to analyze the endpoints and assessments related to safety.

6.3 Per Protocol Analysis Set

The Per-protocol Analysis Set (PPAS) includes all FAS participants who have no major protocol deviations challenging the validity of their data. The PPAS will be used for supplementary analysis of the primary endpoint. Participants will be analyzed according to the treatment received. Major deviations that challenge the validity of the data will be identified by a blinded review and determination of the PPAS will be completed prior to the unblinding of the study for the Week 24 primary analysis.

[redacted]

6.5 Pharmacokinetic/Pharmacodynamic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all participants who receive at least one dose pegloticase and have at least one quantifiable serum PK observation post-first dose. For the OL Pegloticase + MTX Period, only participants in the PK Analysis Set during the DB Pegloticase + MTX Period who enter the OL Period will be included in the analyses.

This analysis set will be used for PK analysis.

6.6 Interim Analyses Set

Not applicable.

6.7 Study-specific Analysis Sets

6.7.1 MTX Analysis Set

The MTX Analysis Set (MAS) includes all participants who received at least 1 dose of MTX in this trial. This analysis set will be used for analyses of safety data during the MTX Run-in Period prior to Day 1 pegloticase and for analysis of MTX polyglutamates.

6.7.2 Any Pegloticase 16 mg Analysis Set

The Any Pegloticase 16 mg Analysis Set includes all participants who receive at least 1 dose of pegloticase 16 mg during either the DB Pegloticase+MTX Period or the OL Pegloticase+MTX Period.

This analysis set will be used for analysis of safety data during the entire DB and OL periods.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

There is no interim analysis planned, and no early stopping guidelines were set up.

7.2 Primary Analysis

The primary analysis will be conducted after all participants complete the Week 24 Visit, the timepoint for the primary efficacy endpoint, in the DB Pegloticase + MTX period or terminate early from the trial prior to Week 24, and the data have been entered, cleaned, and locked. The objective of the primary analysis is to assess complete efficacy and safety data through Week 24 and available data from the OL period at the time of the analysis. The Sponsor (except for selected designees) and vendors involved in clinical operations and data management will remain blinded until after the database lock for the primary analysis following completion of all participants in the DB Pegloticase + MTX Period.

7.3 Final Analysis

The final analysis will occur when target enrollment is complete, and all participants have completed the trial through the 3-month FU (follow up) Visit. Final analysis is based on final locked database to prevent future change. With the exception of the unblinded pharmacist/designee, all investigative site staff directly involved in this trial will remain blinded from randomization through analysis of the final data and all site close-out visits.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will receive and store all data to be used in the planned analyses. This study will use the RAVE database, central laboratory data, PK, antibody, and deviation data. The database is as outlined in the Clinical Data Management Plan (DMP), see details of this section in the DMP.

8.3 Handling of Missing and Incomplete Data

Missing and incomplete dates in AEs and concomitant medications will be imputed as outlined in Appendix G. Partial or missing death dates will be imputed prior to derivation of any endpoint that utilizes the date of death. Missing data in efficacy endpoints will be handled using methods described in Section 9.5.

8.4 Detection of Bias

This study has been designed to minimize potential bias by allocating treatment groups randomly, assessing endpoints and handling withdrawals without knowledge of the treatment. Other factors that may bias the results, such as major deviations, investigational product non-compliance, and reasons for early withdrawal from treatment and study will be assessed and summarized.

8.5 Outliers

Outliers due to data entry errors will be corrected by the study team prior to unblinding data for analysis. The validity of any questionable values or outliers will be confirmed. Outliers or any questionable values with confirmed validity will be included in the analyses presented in this statistical analysis plan unless there is sufficient justification to exclude them. However, ad-hoc sensitivity analyses may be conducted to evaluate the influence of extreme values in the data.

8.6 Distributional Characteristics

Continuous endpoints of change or percent change from baseline value will be analyzed under normality assumption. Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required, data transformation or alternative non-parametric methods of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and outputs will be verified in accordance with current risk-based quality control procedures.

Datasets, tables, figures, and listings will be produced and validated in accordance with SOP-430399. Standard macros will be used when available.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, and biomarker data. Descriptive statistics on continuous data will include mean, median, Q1 (first quartile), Q3 (third quartile), standard deviation and range, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

Confidence intervals (CI) for proportions will be estimated using an exact method proposed by Clopper-Pearson (1934). Kaplan-Meier methods will be used to estimate the median and percentiles for time to event endpoints with CI calculated using the Brookmeyer and Crowley (1982) method.

Further, tabular summaries will be presented by treatment group and treatment period (MTX Run-In Period, DB Pegloticase + MTX Period, and OL Pegloticase + MTX Period). For the MTX Run-in Period, data will be summarized overall for MAS. For the DB Pegloticase + MTX Period, which occurs from Day 1 to Week 24 (prior to infusion at Week 24), data will be summarized by treatment group: pegloticase 16 mg Q4W with MTX and pegloticase 8 mg Q2W with MTX. For the OL Pegloticase + MTX Period, which occurs from Week 24 (starting from infusion at Week 24) to 48, summaries will be presented only for those who enter this period by participant's DB treatment group (pegloticase 16 mg Q4W with MTX, pegloticase 8 mg Q2W with MTX) assignment. AE summaries for the OL Period will be presented by DB treatment group and overall.

To control the overall Type I error rate of the trial at α=0.05, the secondary efficacy endpoint will be tested at the 1-sided Type I error rate of 0.025 sequentially only if noninferiority is achieved for the primary efficacy endpoint at the 1-sided Type I error rate of 0.025. [redacted]

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). For the purposes of analysis, the End of Study/Early Termination (ET) Visit, and the End of

Pegloticase Infusion Visit will be windowed to a visit based on the pegloticase study day of occurrence relative to the target day of each scheduled visit. For sUA measurements, unscheduled assessments will also be windowed. The analysis visit window for serum uric acid (sUA) is provided in Appendix F. The details for other analysis visit windows will be included in the Table, Figure and Listing Shell Document (TFLSD).

For additional details on data presentation, refer to the TFLSD.

Data listings will be sorted by treatment group and participant number.

The details for the other analysis visit window rules will be included in the TFLSD.

9.2 Participant Accountability

A summary of participant disposition will be provided including the number of participants in each analysis set. In addition, the number and percent of participants who completed pegloticase treatment, discontinued pegloticase treatment and reasons for discontinuing, completed study, discontinued study and reasons for discontinuation will be summarized by study period (DB and OL) using FAS.

Key study dates for the first participant enrolled, last participant enrolled, and last participant's end of study will also be presented.

The number and percentage of participants randomized will be tabulated by study site.

9.3 Important Protocol Deviations

Protocol Deviations (PDs) are defined by the study team before the first participant's initial visit and updated during the PD reviews throughout the study prior to database lock.

Deviations will be classified as major or minor occurring in the Screening, MTX Run-in Period, DB and OL Pegloticase + MTX Periods, or Follow-up Period. Using the **safety analysis set**, Protocol Deviations will be summarized by classification, treatment group and treatment period.

The final PD list is used to produce the summary of PDs table and the listing of participants with PDs.

9.4 Demographic, Baseline Characteristics, and Medical History

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the FAS.

The characteristics being summarized include: age, age category (< 50 years, >=50 – 64, ≥ 65 years), sex, race, ethnicity, child bearing potential, time since first symptoms of

gout (in years), time since first diagnosis of gout (in years), presence of uric acid crystals confirming diagnosis, number of acute gout flares in joints over the past 12 months, number of acute gout flares in the past 6 months, pattern of flares, typical severity of acute flares, chronic gout synovitis/arthropathy, prior occurrence of tophi, occurrences of overnight stays in the hospital due to gout, occurrence of surgery for gout (excluding arthrocentesis), prior occurrence of kidney stones, number of episodes of renal colic in the past year, kidney function affected by gout historically, urate lowering therapy history, tobacco use history, current tobacco use status, alcohol use, other substance use, weight, height, BMI and BSA.

Age, time since first symptoms of gout, time since first diagnosis of gout, number of gout flares over the past 12 months, number of acute flares in the past 6 months, number of episodes of renal colic in the past year, baseline weight, height, BMI, and BSA will be summarized as continuous variables showing number of non-missing values, mean, standard deviation, median, Q1, Q3, minimum and maximum. For number of flares, if the result is '>X', the qualifier will be dropped and the numeric value used in the analysis.

Age category, sex, race, presence of uric acid crystals confirming diagnosis, number of gout flares over the past 12 months (1 flare, 2 flares, 3-5 flares, 6-10 flares and > 10 flares), number of acute flares in the past 6 months (1 flare, 2 flares, 3-5 flares, 6-10 flares and > 10 flares), presence of tophi (based on photographic assessment as well as recorded in gout history CRF), chronic gout synovitis/arthropathy, prior occurrence of tophi, occurrences of overnight stays in the hospital due to gout, prior occurrence of kidney stones, kidney function affected by gout, tobacco use history, current tobacco use status, alcohol use, and other substance use will be summarized using categorical values. If multiple races have been reported for a participant, the participant will be categorized as multiple.

Calculations for weight, height, BMI, time since first gout symptoms, and time since first gout diagnosis will be included in the TFLSD.

Medical history information will be coded using Medical Dictionary for Regulatory Activities (MedDRA), summarized, and presented by treatment group and overall for the FAS.

9.5 Efficacy Analyses

Potential intercurrent events (ICEs) like discontinuing from the treatment may occur. Participants who discontinue from the treatment will be encouraged to stay in the trial and are allowed to start other urate lowering therapies. Data will be collected through the planned study completion visit.

In general, treatment policy strategy will be used to account for the ICEs for defining estimands corresponding to continuous efficacy endpoints and tophi resolution endpoints, and a composite strategy will be used for sUA responder endpoints. All efficacy analyses will be based on the observed data except for responder endpoints.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

9.5.1.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

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

Table 9-1. Primary Efficacy Endpoint/Estimand Summary Table

Endpoint/Estimand	Primary Summary and Analysis Method (FAS)	Sensitivity and Supplemental Analyses
Proportion of responders during Month 6	Difference in response rate between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W at Month 6 using g-computation to estimate the covariate-adjusted unconditional treatment effect with 95% CI. A composite strategy will be used to handle ICEs. Participants with missing data during Month 6 and participants who meet the sUA discontinuation criteria (sUA > 6 mg/dL at two consecutive visits) at any time prior to and including Week 24 will be considered non-responders. For all other participants, response will be calculated based on observed data.	Sensitivity: 1) Include sUA results (if available) in the response calculation following discontinuation of treatment due to meeting the sUA discontinuation criteria. 2) Exclude sUA results (treat as missing) after the start of other ULT taken after the first dose of pegloticase. 3) Conduct a tipping point analysis (using Direct Bernoulli Sampling) utilizing a multiple imputation method in participants with missing data during Month 6 who did not meet the sUA discontinuation criteria.

Endpoint/Estimand	Primary Summary and Analysis Method (FAS)	Sensitivity and Supplemental Analyses
		Supplemental: a) Apply an alternative sUA discontinuation criterion in which participants with a single elevated pre-infusion sUA (starting from Week 2) will be considered non-responders. b) Primary efficacy analysis using PPAS.

The primary efficacy analysis will be conducted on the FAS. The proportion of time that the sUA level is below 6 mg/dL is defined as the ratio of the time during which the sUA level remains below 6 mg/dL (using linear interpolation, if necessary) during the entire Month 6 interval (based on all data between pre-dose at Week 20 to pre-dose at Week 24 including unscheduled visits). A participant will be declared a non-responder if the participant had an sUA level > 6 mg/dL at 2 consecutive trial visits prior to or during Month 6 beginning with the Week 2 Visit.

An estimate of proportion of time the sUA < 6 mg/dL will be determined by connecting a participant'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. Analogously, 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. Time between sUA collections will be measured in minutes and converted to hours by dividing by 60.

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 estimated to be below 6 mg/dL.

The proportion of *time P = 100*(W1/T1)*

If the participant's proportion of time where sUA was less than 6 mg/dL, P, is greater than or equal to 80% the participant will be called a responder for the primary efficacy

endpoint. A participant with the proportion of time, P, less than 80% will be counted as a non-responder.

The number and percentage of responders and non-responders will be summarized along with a corresponding 95% CI.

The primary endpoint will be analyzed using g-computation to estimate the baseline covariate adjusted unconditional treatment effect (in terms of response rate difference) with 95% CI using robust variance estimator (Ye et al., 2023). Logistic regression will be used as the working model in the g-computation procedure adjusting for treatment and covariates for presence of tophi (Yes, No), age, baseline weight, baseline ADA status (positive or negative) and baseline estimated glomerular filtration rate (eGFR). The g-computation provides asymptotically normal estimators of unconditional treatment effects in terms of the response rate difference regardless of whether the logistic model is correctly specified. The following steps are used in g-computation to produce an estimator of the covariate adjusted unconditional treatment effect (FDA, 2023):

1. Fit the logistic regression model specified above to the data.
2. For each subject, regardless of treatment assignment, compute the model-based prediction of the probability of response under treatment (pegloticase 16 mg with MTX) using the subject's specific baseline covariates.
3. Estimate the average response rate under treatment by averaging (across all subjects in the trial) the subject-level probabilities estimated in Step 2.
4. For each subject, regardless of treatment assignment, compute the model-based prediction of the probability of response under control (pegloticase 8 mg with MTX) using the subject's specific baseline covariates.
5. Estimate the average response rate under control by averaging (across all subjects in the trial) the subject-level probabilities estimated in Step 4.
6. Use the estimates of average response in the two treatment groups from Steps 3 and 5 to estimate the response rate difference.

The robust variance estimator of the treatment effect will be directly calculated using R package RobinCar. The code for g-computation will be specified in the TFLSD.

The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups ($\pi_c - \pi_t$) is less than the non-inferiority margin of 20%.

The response rate difference estimates and standard errors from the stratified analysis specified above will be used to calculate the non-inferiority p-value from the Z test.

Z = (Response rate Difference estimates – (margin))/standard error. The non-inferiority test p-value will be 1-sided from the Z test above: Pr > Z.

At least two sUA observations from different visits during Month 6 must be available in order for a participant to be eligible for consideration as a responder. Participants with only one sUA observation will be considered non-responders, regardless of the value of that single observation; participants with no sUA values will also be considered non-responders.

In addition, participants who meet the sUA discontinuation criteria (sUA values > 6 mg/dL at 2 consecutive scheduled visits (excluding post-infusion sUA) starting at Week 2 prior to or during Month 6 will be considered to be non-responders. For determination of discontinuation criteria, if both central lab and local lab sUA results are available at a visit then the central lab value will be used for discontinuation criteria determination.

Additionally, the proportion of hours during the period where the sUA was less than 6 mg/dL (based on observed sUA) will be summarized using descriptive statistics (i.e., n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) using the FAS. The number and proportion of participants in the following categories will also be summarized: data available at Week 24 and responders, data available at Week 24 and are non-responders (subcategories for whether or not met stopping rule at or prior to Week 24), and non-responders with data not available at Week 24 (subcategories for if met stopping rule prior to Week 24, or missing data for other reason).

The rationale for using non-responder imputation (NRI) for the primary analysis is based on clinical data indicating that patients who discontinue pegloticase typically experience a rapid rise in serum uric acid (sUA) levels to near-baseline values, suggesting a return to non-responder status (MIRROR-RCT, NCT0399473).

9.5.1.2 Sensitivity Analyses

All sensitivity analyses will use the same logistic regression model and g-computation method as the primary efficacy analysis.

The first sensitivity analysis will include all available sUA results following discontinuation of pegloticase (treatment policy strategy) regardless of meeting the sUA discontinuation criteria and will measure the difference in response rates between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W at Month 6 among all participants who receive pegloticase. Participants who meet the sUA discontinuation criterion may be a responder if they remain in the study and maintain sUA levels < 6 mg/dL.

The second sensitivity analysis will consider two ICEs: meeting sUA discontinuation criterion and initiation of ULTs. Participants who meet the sUA discontinuation criterion prior to/during Month 6 will be considered non-responders, and sUA collected after initiation of ULTs (allowable per the protocol after discontinuation of pegloticase) will be treated as missing. For all other participants, all available sUA during Month 6 will be used in the response calculation (composite strategy).

The sensitivity will examine the handling of missing data during Month 6. A tipping point analysis (via Direct Bernoulli Sampling approach, Yunxia Sui, et. al. (2023)) will be conducted for participants who do not have serum uric acid (sUA) data during Month 6 and who did not meet the sUA discontinuation criteria (sUA > 6 at two consecutive visits starting from Week 2). Participants who meet the discontinuation criterion are considered non-responders, regardless of sUA values available during Month 6 after meeting the discontinuation criteria. A multiple imputation method will be implemented with the following steps:

i. For each participant with missing data during Month 6 who did not meet the discontinuation criteria prior to Month 6, response will be randomly generated independently for each treatment group assuming probability of response ranging between 0-100% by 10% increments.

ii. This will be repeated 1000 times for each 10% increment in assumed response rate.

The proportion of responders will be analyzed using same g-computation approach used in the primary analysis of the primary endpoint to estimate the difference in response rates and the standard error of the response rate difference for each imputed dataset, with associated p-value. Results of the analyses from 1000 datasets for assumed response rates among participants with pegloticase 16 mg Q4W with MTX and pegloticase 8 mg Q2W with MTX will be pooled using Rubin's rule (SAS PROC MIANALYZE) to determine when the response rate in the 16 mg Q4W with MTX group becomes inferior to the response rate in the pegloticase 8 mg Q2W with MTX group.

9.5.1.3 Supplemental Estimand for the Primary Endpoint

For the primary endpoint analysis, participants who meet the sUA discontinuation criteria (sUA values > 6 mg/dL at 2 consecutive scheduled visits excluding post-infusion values at infusion visits) starting at Week 2 are considered non-responders during Month 6. In a real-world setting, some physicians may choose to discontinue pegloticase if participants have a single sUA value > 6 mg/dL. A supplemental analysis will be performed using an

alternative discontinuation criterion, in which participants with a single sUA value > 6 mg/dL, excluding post-infusion values, starting at Week 2 will be considered non-responders for Month 6. This analysis will use the same g-computation method as the primary analysis of the primary endpoint to estimate the difference in response rates and the standard error of the response rate difference.

The proportion of responders at Month 6 will also be analyzed using PPAS. The difference in response rate between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W at Month 6 will be assessed using g-computation to estimate the covariate adjusted unconditional treatment effect with 95% CI.

9.5.2 Analyses of Secondary Efficacy Endpoint/Estimand

Table 9-2. Secondary Efficacy Endpoint/Estimand Summary Table

Endpoint/Estimand	Primary Summary and Analysis Method (FAS)	Sensitivity Analyses
Proportion of participants with complete resolution of ≥ 1 tophus (using digital photography) at Week 24 in participants with tophi at Baseline	Difference in the proportion of participants with complete resolution of ≥ 1 tophus at Week 24 between pegloticase 16 mg Q4W with MTX versus pegloticase 8 mg Q2W with MTX using g-computation to estimate the covariate adjusted unconditional treatment effect with 95% CI. Missing data will be imputed using the modified non-responder imputation method described below. The treatment policy strategy outlined in Section 2.1 will be implemented to handle ICE.	A composite strategy will be used in which participants who meet the sUA discontinuation criterion anytime at/prior to week 24, or have no tophi assessments at Week 24, are considered treatment failures.

Digital photography will be used to assess tophi. Other anatomical sites with large tophi may be photographed in addition to the hands and feet at the Investigator's discretion. All measurable tophi will be measured bi-dimensionally (using the longest diameter and the longest perpendicular to that diameter) and the response of each individual tophus will be categorized according to the change from baseline in area of each tophus at each visit as follows:

Complete Response (CR) – A 100% decrease in the area of the tophus

Marked Response (MR) – At least a 75% decrease in the area of the tophus

Partial Response (PR) – At least a 50% decrease in the area of the tophus

Stable Disease (SD) – Neither a 50% decrease nor a 25% increase in the area of the tophus can be demonstrated

Progressive Disease (PD) – A 25% or more increase in the area of the tophus

Unable to Evaluate –The tophus cannot be accurately measured for any reason at any given post-baseline time point (e.g., image missing or of poor quality, obvious infection of the tophus).

Each individual unmeasured tophus will be semi-quantitatively assessed based upon the impression of the central reader (independent and blinded) using the following guideline:

Complete Response - the disappearance of the tophus.

Improved - An approximate 50% or more reduction from baseline in the size of the tophus.

Stable Disease – Neither improvement nor progression from baseline can be determined

Progressive Disease - An approximate 50% or more increase from baseline in the area of the tophus

Unable to Evaluate - The tophus cannot be assessed for any reason at any given post-baseline time point (e.g., image missing or of poor quality, or obvious infection of the tophus).

Each tophus is assessed by 2 readers. For measurable tophi, the average measurements from the two readers will be computed and the response category will be based on the increase or decrease in the average area. For unmeasurable tophi, the worst response between the two readers will be used in analysis.

The overall response for a participant at a visit will be based upon the best response among all evaluable tophi (including measurable and unmeasured) for that participant at the visit (e.g., if any one tophus shows complete response, the overall response is Complete Response). If any single tophus shows progression, or if a new tophus appears during the study after Day 1 (as identified on the digital photograph in a site previously photographed), the overall response for that participant will be Progressive Disease at the visit, regardless of the response of any other tophi. In general, the overall response assignment is based on the measured or unmeasured tophi category. However, if the best response at a visit for is either “Marked Response” or “Partial Response” (for measurable tophi) or “Improved” (for unmeasurable tophi) then the corresponding overall response will be “Partial Response”.

The proportion of participants with resolution of ≥ 1 tophus (100% decrease in the area of at least 1 tophus) at Week 24 will be analyzed using the same g-computation procedure used for the primary endpoint to estimate the covariate adjusted unconditional

treatment effect with 95% CI. Logistic regression will be used as the working model in the g-computation procedure with treatment and covariates for age, baseline **weight, baseline** ADA and baseline eGFR, **as appropriate**. The pegloticase 16 mg Q4W with MTX group will be shown to be non-inferior to pegloticase 8 mg Q2W with MTX if the upper bound of the 2-sided 95% CI for the difference between the 2 treatment groups is less than the non-inferiority margin of 15%.

In MIRROR-RCT (NCT0399473), the pegloticase 8 mg Q2W + MTX co-administration group exhibited a tophus resolution rate of 35% at Week 24 compared to 13% in the pegloticase 8 mg Q2W monotherapy group (between-group difference [95% CI]: 21% [3%, 39%]) in participants with tophi at baseline (N=52 and 29, respectively). While there are no prior placebo-controlled trials with active control, untreated participants would not be expected to have tophus resolution. Considering an effect size of 30% compared with placebo, a non-inferiority margin of 15% was chosen to preserve 50% of the effect vs. placebo.

The modified non-responder approach will be used for dealing with participants missing tophi evaluation data at Week 24. The imputation, as described below, will be done for overall response and not at the individual tophi level.

Modified non-responder imputation:

Completely missing results post-baseline – 'Progressive Disease' imputed as participants' Overall Response.

Completely missing result at visit but photography was attempted at a prior visit – One-worse than the last evaluable Overall Response is imputed, per Table 9-2.

Photography was attempted at visit, but result was unevaluable: One-worse than the last evaluable Overall Response is imputed per Table 9-3.

Table 9-3. Imputation of One-worse than the Last Evaluable Overall Response

Last Evaluable Overall Response	**Week 24 Imputed Overall Response**
Complete Response	Partial Response
Partial Response	Stable Disease
Stable Disease	Progressive Disease
Progressive Disease	Progressive Disease
No prior post-baseline evaluable response available	Progressive Disease

For the analyses of the overall response at each visit, each category (CR, PR, SD, or PD) will be assigned an ordinal score of 1, 2, 3, or 4. A proportional odds logistic model for ordered categorical data with treatment group as the effect will be used to compare between 2 treatment groups. This will be performed for both the imputed data and the observed data. The estimate of the common odds ratio comparing pegloticase 16 mg Q4W with MTX and pegloticase 8 mg Q2W with MTX will be provided along with the corresponding 95% CI.

9.5.2.1 Sensitivity Analysis

Using the same estimand framework as specified for the primary analysis of the primary endpoint, the sensitivity analysis for the complete resolution of ≥1 tophus during the double-blind pegloticase + MTX period will be performed in the same scenario as the primary efficacy endpoint using the g-computation method described in section 9.5.1.1 above classifying the participants who meet the sUA discontinuation criteria or lack of tophi assessments as the non-responders at Week 24.

9.5.3 Analyses of Exploratory Efficacy Endpoint/Estimand

Table 9-4. Exploratory Efficacy Endpoint Summary Table

Endpoint	Summary and Analysis Method
[redacted]	

Endpoint	Summary and Analysis Method
[redacted]	

Endpoint	Summary and Analysis Method
[redacted]	

Endpoint	Summary and Analysis Method
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Endpoint	Summary and Analysis Method
[redacted]	

Endpoint	Summary and Analysis Method
[redacted]	

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoints

Unless otherwise specified, statistical analyses on safety endpoints will be done using participants from the Safety Analysis Set, which includes participants that are enrolled and received pegloticase.

9.6.2 Adverse Events

MedDRA version 26.1 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The participant incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuation of investigational product, fatal adverse events, and adverse events of interest.

TEAEs during the MTX Run-in Period are defined as adverse events that begin or worsen in severity on or after the date of first dose of MTX (and prior to the first injection date and time of pegloticase at Day 1) through 30 days after the last dose of MTX for participants who do not receive pegloticase.

TEAEs for the DB Pegloticase + MTX Period are defined as events that occur on or after the start date and time of the first pegloticase infusion through 30 days after the last dose of MTX or pegloticase/placebo for pegloticase (whichever is later) prior to Week 24 (and prior to the first dose of OL pegloticase for participants who enter the OL Pegloticase + MTX Period).

TEAEs during the OL Pegloticase + MTX period are defined as adverse events that begin or worsen in severity on or after the date of first pegloticase infusion in the OL period (i.e. infusion of pegloticase at Week 24) through 30 days after the last dose of pegloticase and/or MTX (whichever is later). Events with an onset date equal to the Week 24 infusion date and with missing start time will be considered treatment emergent in the OL Pegloticase + MTX Period.

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

All AEs, both serious and non-serious, will be assessed for severity using the Rheumatology Common Toxicity Criteria (CTC) v2.0. AEs will be coded using the most recent version of MedDRA. Summaries (overall, SOC/PT and exposure-adjusted) of TEAEs in the Run-in Period, DB and OL Pegloticase + MTX Periods and in Safety Follow-up Period will be provided for the MAS (for Run-in Period) and Safety Analysis Set (subset to those entering each period for the DB, OL and follow-up periods.

The number and percentage of participants reporting TEAEs will be summarized by SOC and PT, severity, and relationship to the study drug. The number and percentage of participants reporting SAEs will also be summarized. If a participant reports multiple occurrences of the same AE, the highest recorded severity will be taken as the severity in the summary.

In addition, an overall summary table will be produced showing the number and percentage of participants with at least 1 TEAE in any of the following categories for each period for the MTX and Safety analysis sets and over both the DB and OL periods combined for the Any Pegloticase 16 mg Analysis Set:

- TEAEs
- Serious TEAEs
- TEAEs related to MTX
- TEAEs related to pegloticase (applicable to DB and OL Pegloticase + MTX Periods only)
- Serious TEAEs related to MTX
- Serious TEAEs related to pegloticase (applicable to DB and OL Pegloticase + MTX Periods only)
- TEAEs with a Rheumatology CTC Criteria of 3 or higher
- TEAEs leading to permanent withdrawal of MTX
- TEAEs leading to permanent withdrawal of pegloticase (applicable to DB and OL Pegloticase + MTX Periods only)
- TEAEs related to MTX leading to permanent withdrawal of MTX
- TEAEs related to pegloticase leading to permanent withdrawal of pegloticase (applicable to DB and OL Pegloticase + MTX Periods only)

- TEAEs leading to death
- TEAEs of special interest (adjudicated infusion reactions [IRs], adjudicated anaphylaxis, gout flares, and adjudicated major adverse cardiovascular events)

For the DB and OL Pegloticase + MTX Periods, the number and percentage of participants as well as the number of events with any infusion reactions including/excluding anaphylaxis will be included in the summary.

Using the Safety Analysis Set, an overall summary of AEs occurring during the DB and OL follow-up periods (with onset more than 30 days after the last dose of study medication), including the number and percentage of participants with each AE type as well as the number of events will be summarized for each of the following:

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

Percentages for the overall summary of AEs during follow-up will be based on the number of participants 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 and percentage of participants experiencing TEAEs for the following:

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

Summaries of TEAEs by maximum severity, overall and by SOC and PT, and Serious TEAES overall and by SOC and PT will also be summarized for both the DB and OL Pegloticase + MTX Periods combined for the Any Pegloticase 16 mg Analysis Set.

The exposure-adjusted incidence rate (EAIR) will be calculated based on MTX exposure and pegloticase exposure and will be summarized for DB Pegloticase + MTX Periods, respectively in the following tables:

- TEAEs Overall summary
- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT

For the DB Pegloticase + MTX Period, **person years (PY)** is defined for MTX and pegloticase separately as:

- For participants with the event, PY = the date of the first occurrence of the event – the date of the first dose of treatment in the DB Pegloticase + MTX Period.
- For participants without the event,
  - PY = the date of last treatment – date of first treatment in DB Pegloticase + MTX Period + 1 for participants who do not enter the OL Period, and
  - PY = the date of the first treatment during the OL Pegloticase + MTX Period – date of first treatment in DB Pegloticase + MTX Period + 1 for participants who enter the OL Period.

The PY were summed over all participants exposed to study drug in each treatment group and divided by 365.25 to get the total PY of exposure for each event. The EAIR is calculated as the total number of participants with the event divided by the person-years (PY) of exposure for the event.

Listings will be provided for serious AEs and AEs of special interest (IRs, Anaphylaxis, MACE).

9.6.2.1 Adverse Events of Special Interest (AESIs)

AESIs – including IRs, anaphylaxis, gout flares, and major adverse cardiovascular events (MACE) **– will be summarized using both** the while-on-treatment **and while-on-study approaches for the defined periods.**

For the while-on-treatment approach, incidence for each AESI will be summarized for DB, OL **and DB + OL** pegloticase + MTX periods**. In addition,** incidence rates and EAIRs will be calculated, along with 95% CIs of the between-treatment group difference.

For the while-on-study approach, event counting periods are defined as: DB period = (first DB dose date to the earliest of [EOS, first OL dose date]); and Entire

Study period= (first DB dose date to EOS), For each AESI, incidence rate will be summarized for DB and entire study periods. In addition, subject incidence and SAIRs will be calculated, along with 95% CIs between-treatment group difference.

An independent external adjudication committee will review and adjudicate reported events infusion reaction, MACE, and anaphylaxis. The AESI of gout flare will not be adjudicated.

Infusion Reactions (IR) and Anaphylaxis

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

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

Signs and symptoms of the IR/anaphylaxis are recorded in the eCRF. The investigator reported and adjudicated events, and the associated signs and symptoms, will be summarized separately by SOC and PT for each category above. Events will also be summarized by severity and the time relative to the most recent pegloticase infusion for each category above. Time relative to the most recent pegloticase infusion will be categorized as: during infusion, ≤ 2 hours after infusion, > 2 hours to 24 hours after infusion, > 24 hours after infusion, and missing. The summary of time relative to the most recent pegloticase infusion will also be summarized for both the DB and OL Pegloticase + MTX Periods combined for the Any Pegloticase 16 mg Analysis Set. Serious events and the associated symptoms will be summarized by SOC and PT. The number of events per participant, the number of events and serious events per infusion, and the number of participants with the first event by infusion number will be summarized as well for each category. IRs (including anaphylaxis) that occur on the same date will be considered one event.

In addition, the number and percentage of participants with adjudicated infusion reactions including anaphylaxis will be summarized overall and by severity of event by the following categories for both anti-PEG and anti-uricase antibodies:

- Anti-drug antibody (ADA) status at baseline (positive or negative)
- Treatment-emergent ADA status (positive or negative) [defined in Section 9.6.7] using the status during the DB Pegloticase + MTX Period for IRs that occur in that period and using the overall ADA status for entire study for IRs that occur during the OL Pegloticase + MTX Period

Major Adverse Cardiovascular Events

MACE includes non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure.

The following search algorithm will be used to identify possible MACE based on the Amgen Adverse Medical Query (AMQ) in reference to the Standardized MedDRA Queries (SMQ):

- For cardiovascular death (for fatal cases only):
  - AMQ: Myocardial infarction (broad), Ischemic Central Nervous System (CNS) Vascular conditions (narrow); Hemorrhagic central nervous system vascular conditions (narrow), Central nervous system vascular disorders, not specified as hemorrhagic or ischemic (narrow), Embolic and thrombotic events (arterial, venous, vessel type unspecified and mixed arterial and venous) (narrow), Cardiac failure (broad), Torsade de pointes, shock-associated conditions (SMQ) (narrow), Arrhythmia related investigations, signs and symptoms (broad), Cardiomyopathy (broad), Supraventricular tachyarrhythmias (narrow), Ventricular tachyarrhythmias (narrow), Conduction defects (narrow)
  - All PTs under SOC of Cardiac disorders
  - High level group term (HLGT) Aneurysm
- For non-fatal myocardial infarction: SMQ Myocardial infarction (broad)
- For non-fatal stroke: AMQ Ischemic Central Nervous System (CNS) Vascular conditions (narrow); Hemorrhagic central nervous system vascular conditions (narrow); Central nervous system vascular disorders, not specified as hemorrhagic or ischemic (narrow)
- Congestive heart failure: SMQ Cardiac failure (broad)

Using the MAS and Safety Analysis Set, the cardiovascular events identified using the aforementioned criteria as well as the adjudicated cardiovascular events will be summarized by SOC and PT for the Run-in Period, DB and OL Pegloticase + MTX Periods by treatment group. Adjudicated MACE will also be summarized for both the DB and OL Pegloticase + MTX Periods combined for the Any Pegloticase 16 mg Analysis Set.

Gout Flares

The number and percentage of participants who experienced a gout flare and number of gout flares per participant during the Run-in Period, DB and OL Pegloticase + MTX Periods (recorded in the AE eCRF) will be provided for the Safety Analysis Set . Events are summarized for each period according to the onset date of the flare, and only summarized in the period of onset. Additionally, the incidence of flares per month of the

DB Pegloticase + MTX Period and for the periods from Day 1 to Week 12 and Week 12 to Week 24 will be summarized.

9.6.2.2 Exploratory Safety Endpoints

9.6.3 Laboratory Test Results

Clinical laboratory test results (hematology and chemistry,) and their changes from baseline will be summarized by visit and treatment group and treatment period on the Safety Analysis Set using descriptive statistics. Only data collected within 30 days of the last dose of MTX and/or pegloticase, whichever is later, will be included. Results from the Follow-up visits will also be summarized.

If the value is reported as '< a', '> a', '≤ a' or '≥ a', then the value will be imputed as 'a' before the analysis. Observed values will be compared to the relevant normal reference range and classified as low (below the lower range), normal (within the range or on the

limit) or high (above the upper range). The observed values falling outside the normal reference ranges will be flagged.

For tests where the Common Terminology Criteria for Adverse Events (CTCAE) is available, shift tables will be based on the CTCAE grade comparing baseline grades with grades at post-baseline worst grade for the study period.

Summary of liver function test (LFT) abnormalities on alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL) and alkaline phosphatase (ALP) will be presented by study period and the treatment group. The number and percentage of participants who meet Hy's law will also be summarized by treatment group for the DB and OL periods.

9.6.4 Vital Signs

The observed values along with the changes from baseline will be summarized by treatment group and treatment period for systolic blood pressure, diastolic blood pressure, body temperature, heart rate, and respiratory rate visit using the Safety Analysis Set.

Analyses will include data collected within 30 days of the last dose of MTX and/or pegloticase, whichever is later, and available data at the follow-up visits.

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

9.6.5 Physical Measurements

No summarizations of the physical examination data will be presented.

9.6.6 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at Screening and at the discretion of the Investigator thereafter. When possible, a 12-lead ECG will also be performed when an AESI of IR, anaphylaxis or cardiovascular event is suspected. No summaries of ECG data will be performed.

9.6.7 Antibody Formation

The number and percentage of participants ADA positive and ADA negative at baseline will be summarized by treatment group for anti-PEG and anti-uricase antibodies using the Safety Analysis Set. Additionally, the number and percentage of participants who meet the following criteria will be summarized each treatment period by treatment group for anti-PEG and anti-uricase antibodies:

DB Pegloticase + MTX Period

- Antibody positive at any time (ADA prevalence)
- Treatment-induced antibody positive, defined as ADA positive with ADA negative (or missing) at baseline
- Treatment-boosted antibody positive, defined as a 4-fold increase in titer from baseline titer
- Treatment-emergent (TE) ADA positive: ADA positive in participants ADA negative (or missing) at baseline, or with a 4-fold increase in titer from baseline
- TE ADA negative: ADA negative or with titer less than a 4-fold increase from baseline titer
- Transient, defined as ADA negative result at the subject's last timepoint tested in participants who are treatment-emergent ADA positive at any timepoint during the period.

Except for transient, the other parameters listed above will include ADA results collected up to 3 months (90 days) after the last pegloticase infusion for participants who prematurely discontinue pegloticase prior to Week 24, and through Week 24 only for participants who complete treatment through Week 24. The transient summary will be assessed using all available results through the end of study participation.

Open-Label Pegloticase + MTX Period + 3-Month Follow-Up

- Antibody positive at any time (ADA prevalence)
- Treatment-induced antibody, defined as ADA positive in participants TE ADA negative through Week 24
- Treatment-boosted antibody positive, defined as a 4-fold increase in titer from baseline titer in participants TE ADA negative through Week 24
- TE ADA positive: ADA positive or with a 4-fold increase in titer from baseline titer in participants treatment-emergent ADA negative through Week 24
- TE ADA negative: TE ADA negative through Week 24 and ADA negative or with titer less than a 4-fold increase from baseline titer during the OL period
- Transient, defined as ADA negative result at the subject's last timepoint in participants who are treatment-emergent ADA positive at any timepoint during the period (including through the 3-month follow-up visit).

Only results from visits after Week 24 will be included for analyses of the OL period. Additionally, each of the above parameters will be summarized for the study overall, using the same definitions as for the DB Pegloticase + MTX Period, but assessed using ADA results during the entire study.

Anti-PEG and anti-uricase titer will be summarized descriptively with mean and CV% by study visit. Kaplan-Meier estimates of the time to treatment-emergent ADA positive result will be produced for anti-PEG and anti-uricase during DB period.

ADA results will be included in a subject listing. The listing will include the TE ADA status at each timepoint.

9.6.8 Exposure to Investigational Product

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol.

Study drug exposure will be summarized from the MTX dosing calendar using the duration of treatment (in days), number of infusions, total dose (mg) received for MTX and pegloticase, average dose (mg) received for MTX during MTX Run-in, and during the DB and OL Pegloticase + MTX Periods, and total dose (mg) per dose overall. The MTX is supposed to be taken once weekly. Any split doses taken within 48 hours are considered as one single dose, and the sum of the split doses is considered as the dosage for that dose number. The usage of folic acid, IR prophylaxis of fexofenadine in the evening prior to pegloticase infusion, IR prophylaxis of fexofenadine in the morning prior to the pegloticase infusion, acetaminophen, and methylprednisolone on the morning prior to pegloticase infusion will be summarized by number of participants and percentage with compliance < 80% and ≥ 80%.

The duration of treatment for each treatment period will be defined as following using the Safety Analysis Set:

During MTX Run-in Period, the duration of MTX is defined as (the last dose of MTX prior to the Day 1 visit date – first dose date of MTX) + 1.

During Pegloticase + MTX Periods, the duration of treatment will be summarized by treatment group separately for the DB and OL Pegloticase + MTX Periods:

Duration of MTX dosing in the given period is defined as [the last MTX date – first MTX dosing date] + 1

Duration of pegloticase dosing in the given period is defined as [the last pegloticase infusion date– first pegloticase infusion date] + 1

Overall duration of treatment will be summarized as follows:

Duration of MTX dosing is defined as [the last MTX date – first MTX dosing date (on or after the date of the Day 1 visit)] + 1

The total MTX dose (mg) received, the average MTX dose (mg), and the number of participants with dose reductions (reduction in planned dose for reason of AE, abnormal

labs, or titration down) from planned 15 mg/week will be summarized with descriptive statistics by treatment group and treatment period.

The number of pegloticase infusions received overall per participant, the number of incomplete infusions received, and number of interrupted infusions with frequency will be summarized by treatment group for the DB and OL Pegloticase + MTX Periods.

Adherence to Pegloticase

Other than the summarizations of pegloticase infusions, the compliance with pegloticase will also be summarized.

Adherence to Methotrexate

Compliance with MTX 15 mg will be summarized based on drug accountability data for the Safety Analysis Set for the duration of the study in MTX Run-in Period+ DB period, and in OL period. Compliance will be calculated as 100 x (the number of capsules taken divided by the expected number of capsules). Participants are expected to take 6 capsules (15 mg) each week.

The number of capsules taken is defined as the number of capsules dispensed – number of capsules returned. If a bottle is not returned, it will be assumed that the participant took all pills in the bottle and the number of capsules returned is set to 0.

Additionally, compliance with MTX during the Run-in + DB period and MTX during OL periods will be calculated from the MTX calendar log (a dosing dairy where participants recorded date, time and # of capsules taken each week). Compliance based on diary data is defined as 100 x (number of MTX doses taken divided by the number of expected doses). The number of MTX doses taken will be calculated by taking the number of MTX doses taken starting with the two most recent doses prior to the first pegloticase infusion up through the last pegloticase infusion. The expected number of doses is 2 times the number of pegloticase infusions received (as participants should take 2 MTX doses in between each infusion).

9.6.9 Exposure to Non-investigational Product

Not Applicable

9.6.10 Exposure to Concomitant Medication

Number (%) of participants who received prior medications and concomitant medications will be summarized by World Health Organization Drug dictionary (WHODD). Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical

(ATC) drug class Level 4 and preferred name. At each level of summarization, a participant is counted once if the participant reported one or more medications at that level. The summary will be ordered alphabetically by ATC medical class and then alphabetically by preferred term within each ATC medical class.

Prior medications are defined as medications with a start date occurring before the first MTX administration date. Medications that start prior to MTX administration that are ongoing or have a stop date after the first MTX date may be considered as both prior and concomitant.

Concomitant medications in the MTX Run-in Period are defined with respect to the first dose of MTX at Week -4. Concomitant medications in the DB and OL Pegloticase + MTX Periods are defined with respect to the first dose of pegloticase in that treatment period.

Concomitant medications for MTX Run-in Period are defined as:

1) Medications started on or after the first MTX dose date in this period and prior to the first dose of pegloticase, or within 30 days of the last dose of MTX for participants who do not receive pegloticase, or
2) Medications started before the first MTX dose date, in the period and that are ongoing or have an end date after the first MTX dose date in this period

Concomitant medications for DB and OL Pegloticase + MTX Periods are defined as:

1) Medications started on or after the first pegloticase infusion date and within 30 days of the last pegloticase infusion or MTX dose within that period
2) Medications started before the first pegloticase infusion date, and that are ongoing or have an end date after the first pegloticase infusion date within that period

The missing start/stop date will be imputed as appropriate, and the details of the imputation will be included in the TFLSD.

Summaries of prior and concomitant medications will be presented by treatment group, treatment period, and overall for the Safety Analysis Set.

9.7 Other Analyses

Other analyses in the study include analyses for PK endpoints, and biomarker endpoints.

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/ Pharmacodynamic Endpoints

Nominal sampling times will be used for individual concentration-time plots and tables. Individual concentration-time data will be tabulated and presented graphically. Summary of Pegloticase and MTX PK concentrations over time will be provided. Mean

concentration-time profiles for each dose will be provided. The reason for excluding any sample from the analyses will be provided. PK analyses will be provided by Amgen Clinical Pharmacology, Modeling & Simulation (CPMS).

For the summary of pegloticase concentrations, all other concentrations below the limit of quantification (BLQ) will be imputed as half of the lower limit of quantification value. Samples collected more than 31 days after the participant's last pegloticase infusion are excluded from the analysis.

Concentrations of MTX polyglutamate are measured for 5 active metabolites (MTX-PG1, MTX-PG2, MTX-PG3, MTX-PG4, MTX-PG5). Concentrations will be summarized for each of the individual metabolites, the sum of MTX-PG1 and MTX-PG2, the sum of MTX-PG3, MTX-PG4, and MTX-PG5, the sum of MTX-PG4 and MTX-PG5, and the sum over all 5 metabolites will be summarized for the MTX Analysis Set overall. All post-baseline concentrations BLQ will be excluded from analysis. When calculating the sum over MTX-PGs, values of '<5' count as 0 in the sum. The number of BLQ values will be presented for pegloticase and MTX polyglutamate concentration summaries.

Concentrations for pegloticase will be summarized by treatment group and treatment period. Further, pegloticase concentrations will be provided by visit and by treatment group by treatment-emergent ADA status (positive vs. negative) for anti-PEG ADA.

9.7.3 Analyses of Health Economic Endpoints

Not applicable.

9.7.4 Analyses of Biomarker Endpoints

Serum, plasma, and urine will be assessed for biomarkers related to the mechanism of action of pegloticase and factors associated with gout activity. Intended purpose and exploratory biomarker analysis include but are not limited to proteomic evaluation of gout-flare inflammatory mediators and cardiometabolic markers to inform trial findings (as needed). Detailed analysis plan for biomarkers will be described in a biomarker analysis plan (BAP).

10. Changes From Protocol-specified Analyses

Two analysis sets, the PPAS and the Any Pegloticase 16 mg Analysis Set, were added which were not specified in the protocol.

11. Literature Citations / References

Arthur Chatton, et al (2020). G-computation, propensity score based methods, and targeted maximum likelihood estimator for causal inference with different covariates sets: a comparative simulation study. *Scientific Reports*, volume 10, Article number: 9219.

Brookmeyer, R. and Crowley, J. (1982). A Confidence Interval for the Median Survival Time, Biometrics, 38, 29 - 41.

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FDA (2023). Adjusting for covariates in randomized clinical trials for drugs and biological products. Guidance for Industry. *Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, Food and Drug Administration*

(FDA), U.S. Department of Health and Human Services, May 2023.

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

Yunxia Sui, et al (2023). Application of Tipping Point Analysis in Clinical Trials using the Multiple Imputation Procedure in SAS; PharmaSUG 2023 - Paper SD-069.

12. Prioritization of Analyses

Not applicable.

13. Data Not Covered by This Plan

Not applicable.

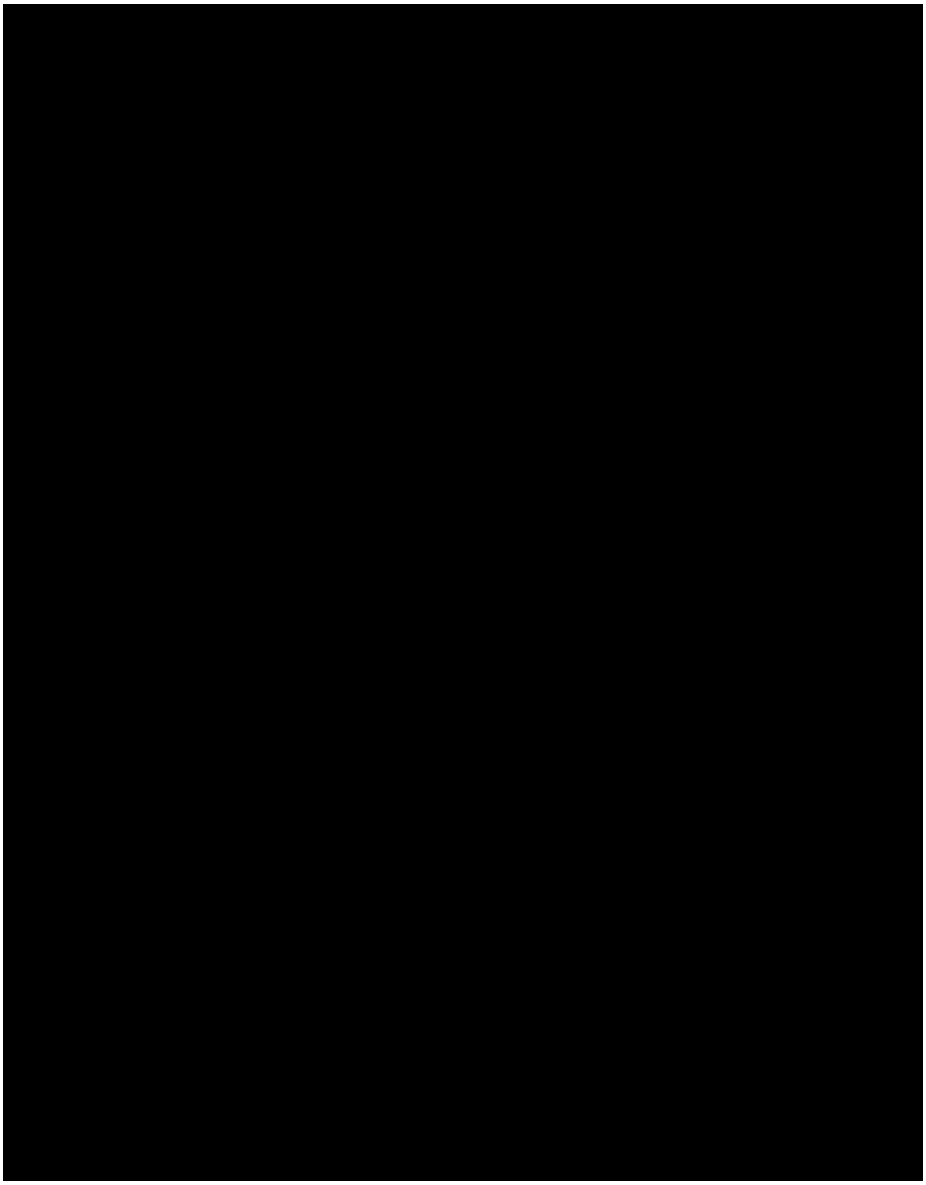
14. Appendices

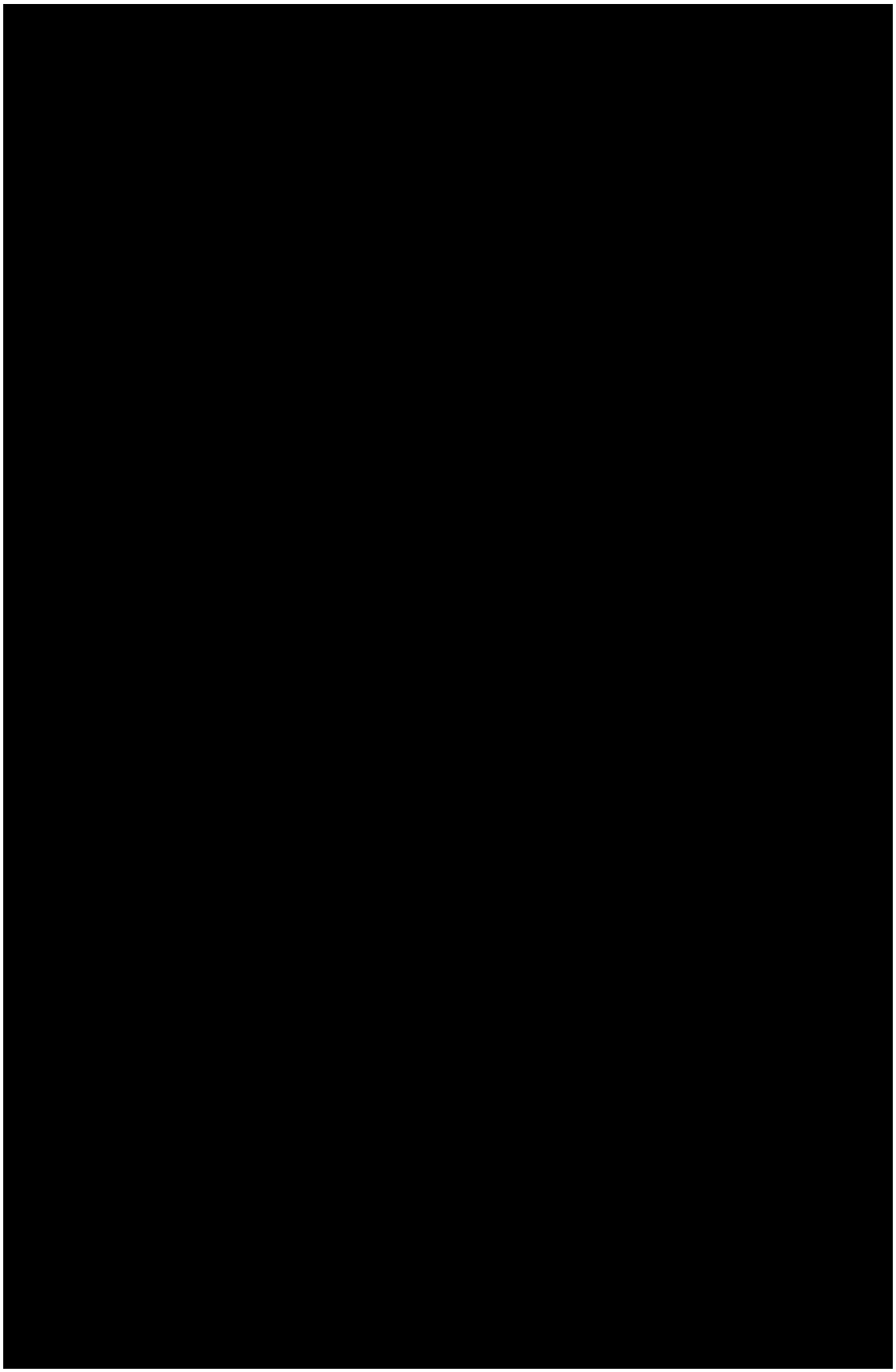
Appendix A. Reference Values/Toxicity Grades

Not applicable.

Appendix B. Concomitant Medications

Not applicable.





Appendix E. Details of PK or PK/PD Methods for Modeling

Not applicable.

Appendix F. Analytical Windows

Analysis 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). For the purposes of analysis, the unscheduled visit, End of Study/Early Termination (ET) Visit, and the End of Pegloticase Infusion Visit will be windowed to a visit based on the pegloticase study day of occurrence relative to the target day of each scheduled visit. In the event that an End of Study/ET or End of Pegloticase visit is reassigned to a visit for which the participant has scheduled data collected, the data from the nominal scheduled visit will take precedence and the data from the unscheduled visit, End of Study/ET or End of Pegloticase visit will not be summarized. For sUA, the unscheduled visits will also be used for the determination of sUA responder.

Table 14-1 Analysis Visit Windows for sUA Collections

Scheduled Visit	Target Day of the Visit	Analysis Visit Window
Day 1	Day 1	Day 1
Week 2	Day 15	Day 2 to Day 22
Week 4	Day 29	Day 23 to Day 36
Week 6	Day 43	Day 37 to Day 50
Week 8	Day 57	Day 51 to Day 64
Week 10	Day 71	Day 65 to Day 78
Week 12	Day 85	Day 79 to Day 92
Week 14	Day 99	Day 93 to Day 106
Week 16	Day 113	Day 107 to Day 120
Week 18	Day 127	Day 121 to Day 134
Week 20	Day 141	Day 135 to Day 144
Week 21	Day 148	Day 145 to Day 151
Week 22	Day 155	Day 152 to Day 158
Week 23	Day 162	Day 159 to Day 165
Week 24	Day 169	Day 166 to Day 176
Week 26	Day 183	Day 177 to Day 190

Scheduled Visit	Target Day of the Visit	Analysis Visit Window
Week 28	Day 197	Day 191 to Day 204
Week 30	Day 211	Day 205 to Day 218
Week 32	Day 225	Day 219 to Day 232
Week 34	Day 239	Day 233 to Day 246
Week 36	Day 253	Day 247 to Day 260
Week 38	Day 267	Day 261 to Day 274
Week 40	Day 281	Day 275 to Day 288
Week 42	Day 295	Day 289 to Day 302
Week 44	Day 309	Day 303 to Day 316
Week 46	Day 323	Day 317 to Day 330
Week 48	Day 337	≥Day 331*

* Up to before post treatment 3-month safety follow up visit.

Appendix G. Handling of Dates, Incomplete Dates and Missing Dates

[Imputation Rules for Partial or Missing Start Dates
The reference date for the following rules is the date of first dose [MTX or Pegloticase as per the case]].

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1=Impute the date of first dose; 2=Impute the first of the month; 3=Impute January 1 of the year; 4=Impute January 1 of the stop year
Note: For participants who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.

Imputation Rules for Partial or Missing Stop Dates

Initial imputation

- If the month and year are present, impute the last day of that month.
- If only the year is present, impute December 31 of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

If the imputed stop date is before the start date, set stop date to missing.

If the imputed stop date is after the death date, impute as death date.

Imputation Rules for Partial or Missing Death Dates

If death year and month are available but day is missing:

- If yyyymm for the date last known to be alive equals yyyymm for death date, set death date to the day after the date last known to be alive.

- If yyyymm for the date last known to be alive is less than the yyyymm for death date, set death date to the first day of the death month.
- If yyyymm for the date last known to be alive is greater than yyyymm for death date, assume death date is in error, do not impute and censor the participant survival time.

If month and day are missing and year of death is known:

- If yyyy for the date last known to be alive equals yyyy for death date, set death date to the day after last known to be alive date.
- If yyyy for the date last known to be alive is less than yyyy for death date, set death date to the first day of the death year.
- If yyyy for the date last known to be alive is greater than yyyy for death date, assume death date is in error, do not impute and censor the participant survival time.

If a death occurred and a death date is totally missing:

- Do not impute and censor the participant survival time.