Statistical Analysis Plan

Sponsor Name: Horizon Therapeutics Ireland DAC

Protocol Number: HZNP-KRY-202
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy and Safety Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled GOut Receiving KRYSTEXXA® (pegloticase) (MIRROR Randomized Controlled Trial [RCT])

Protocol Version and Date: Version 3.0, Amendment 2 (17Mar2021)

[redacted]

SAP Version: 3.0

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
2.0	12-MAY-2021	[redacted]	• Planned analyses revised to remove submission of 6M analysis data and unblinding after second DMC review • Alpha adjustment updated; response rate during Month 9 moved from secondary endpoint to exploratory • Clarifications made to rules for handling missing and impacted data due to COVID-19 for responder analyses • Clarifications added to multiple imputation process • Reorganization of primary endpoint analysis sections in 9.2 to match a protocol amendment; supplemental analysis section added and sensitivity analyses for mITT and PP populations moved to supplemental analysis • Supplemental analysis of response endpoints using logistic regression in imputation model added. • Summary of infusion reactions/anaphylactic reactions by ADA status added; summary of gout flares by 3 month intervals added; summary of AEs occurring on commercial pegloticase or MTX added • Changes from protocol were removed since a protocol amendment incorporated the changes listed in version 1.0 of the SAP.
3.0	23-SEP-2021	[redacted]	• Tipping point analysis added as sensitivity to primary endpoint analysis. • Supplemental analysis for primary endpoint added looking at response when a single sUA > 6 mg/dL stopping rule is applied. • Modifications made to the handling of data in subjects impacted by COVID-19; imputation for primary endpoint will be used only for subjects who have missing data during time of primary endpoint due to site closure from COVID-19. • Clarifications added for the analysis of tophi data. • Compliance calculation for MTX updated. • Other minor clarifications and grammatical corrections made.

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

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1. Glossary of Abbreviations

Abbreviation	Description
°C	degrees Celsius
°F	degrees Fahrenheit
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	Anatomical Therapy Chemical
BMI	body mass index
BSA	body surface area
CI	confidence interval
CMC	CarpoMetaCarpal joint
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CS	clinically significant
CSH	heterogeneous compound symmetry
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DBP	diastolic blood pressure
DECT	dual-energy computed tomography
dL	deciliter
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ET	Early Termination
FCS	fully conditional specification
GCR	gout chronic response
GCR20	gout chronic response – 20% reduction
GCR50	gout chronic response – 50% reduction
GCR70	gout chronic response – 70% reduction

Abbreviation	Description
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
HEENT	head, eyes, ears, nose, throat
HLGT	High-Level Group Term
IMM	Immunomodulator
ICF	Informed Consent Form
ICH	International Committee on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IP	InterPhalangeal joint
IR	infusion reaction
ITT	Intent-to-Treat
IV	intravenously
kg	kilogram
KM	Kaplan-Meier
lb	pound
LS	least squares mean
MACE	Major Adverse Cardiovascular Events
max	maximum
MCP	MetaCarpoPhalangeal joints
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minimum
mITT	Modified Intent-to-Treat
mL	milliliter
mmHg	millimeters mercury
MMRM	mixed model repeated measures
MTP	MetaTarsoPhalangeal joints
MTX	methotrexate
MTX-PG(1-5)	methotrexate polyglutmate metabolites (1 through 5)
n	number of observations
NCS	not clinically significant
NIAID/FAAN	National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria
NSAID	non-steroidal anti-inflammatory drug

Abbreviation	Description
OMERACT	Outcome Measures in Rheumatology
PEG	polyethylene glycol
PIP	Proximal InterPhalangeal joints
PK	pharmacokinetics
PP	Per-protocol
PT	preferred term
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging scoring
Rx	prescription
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
sBLA	supplemental Biologic License Application
sUA	serum uric acid
TEAE	treatment emergent adverse event
TLF	Tables, Listings and Figures
TOEP	Toeplitz
TOEPH	heterogeneous Toeplitz
ULN	upper limit of normal range
ULT	urate lowering therapy
UN	unstructured variance-covariance matrix
VAS	visual analog scale
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-202 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, listings and figures (TLFs) for the HZNP-KRY-202 study, including summaries of concentrations for methotrexate (MTX) polyglutamate, pegloticase, and anti-drug antibodies (ADA). Additional pharmacokinetic (PK) analysis may be performed by a separate vendor and is not covered in the scope of this SAP.

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

2.2. Planned Analyses

2.2.1. Interim Analyses

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform review of unblinded, comparative efficacy and safety data in order to protect subject welfare and preserve study integrity. The scope of the analysis to be provided to the DMC is provided in a mutually agreed upon charter, which defines the DMC membership and meeting logistics.

There are two planned timepoints at which data will be reviewed by the DMC. The first analysis will occur after approximately half of the randomized subjects (i.e. ~78 subjects) have completed 24 weeks of treatment in the Pegloticase + Immunomodulator (IMM) Period or discontinued therapy (or study) prior to that time. The second unblinded, comparative analysis will be performed when all randomized subjects have completed 24 weeks of treatment or discontinued treatment (or study) prior to Week 24.

The main purpose of the analysis by the DMC is to review the safety data. However, limited efficacy data, including the primary efficacy endpoint, will be provided to the DMC for review to assist in assessing risk and benefit. Additionally, some data for the secondary endpoints (response during Month 12) will be included in the second analysis. Even though there is no plan to make an inference of the primary or secondary efficacy endpoints, an alpha adjustment of 0.0005 will be made to account for this analysis. The DMC will recommend to Horizon whether to continue the study with or without modification or stop the study due to safety reasons.

2.2.2. Final Analysis

The primary analysis of all endpoints will be performed after all subjects reach Week 52 in which the primary and secondary efficacy endpoints will be tested at the 0.0495 significance level in

sequential order. All other efficacy endpoints are exploratory in nature and will be tested using 2-sided tests at the 5% significance level without multiplicity adjustment.

A follow-up analysis will be performed after all subjects complete the post-treatment follow-up period. The follow-up analysis will only include descriptive summaries of the post-treatment efficacy and safety data.

In addition to the above analyses, blinded safety data will be summarized regularly throughout the study for safety monitoring by the Sponsor.

2.3. Coronavirus Disease 2019 (COVID-19)

The COVID-19 pandemic outbreak occurred midway through enrollment for this study. This SAP will describe analyses to be performed to assess the impact of COVID-19 on the study and methods for handling missing data due to the effects of COVID-19 on study subjects and sites.

3. Study Objectives

3.1. Primary Objective

The primary objective is to evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the response rate during Month 6 (Weeks 20, 21, 22, 23 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.

3.2. Secondary Objectives

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on 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.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the complete resolution of ≥ 1 tophi (using digital photography) at Week 52 in subjects with tophi at baseline.

- Evaluate the effect of pegloticase and MTX vs. pegloticase and placebo for MTX on the mean change from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) Score at Week 52.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in Health Assessment Questionnaire (HAQ) Pain Score at Week 52.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in HAQ Health Score at Week 52.

3.3. Exploratory Objectives

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in urate volume and bone erosions due to gout to Weeks 14, 24, and 52 based on dual-energy computed tomography (DECT).

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in bone erosions due to gout to Weeks 24 and 52 based on X-rays of the hands and feet.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the complete resolution of ≥ 1 tophi (using digital photography) at Weeks 24 and 36 in subjects with tophi at baseline.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in tophus size (long axis measured using digital photography) to Weeks 14, 24, 36 and 52 in subjects with tophus present at baseline.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on 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.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on 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.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on 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, 21, 22, 23, and 24) combined.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on reducing sUA to < 5 mg/dL for at least 80% of the time during Months 3, 6, 9 and 12, individually.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in sUA at Weeks 14, 24, 36 and 52.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the time to first sUA > 6 mg/dL.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the time to two consecutive sUA > 6 mg/dL (sUA stopping rule).

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the percentage of non-hyperuricemic (sUA < 6 mg/dL) time during Months 3, 6, 9 and 12.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in Health Assessment Questionnaire (HAQ) Pain Score at Weeks 14, 24, and 36.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in HAQ Health Score at Weeks 14, 24, and 36.

- Evaluate the effect of pegloticase and MTX vs. pegloticase and placebo for MTX on the mean change from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) Score at Weeks 14, 24, and 36.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in tender joint count (68-point scale) at Weeks 14, 24, 36 and 52.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in swollen joint count (66-point scale) at Weeks 14, 24, 36 and 52.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in number of tender or swollen joints at Weeks 14, 24, 36 and 52.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in physician global assessment of gout at Weeks 14, 24, 36 and 52.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36 and 52.

- Evaluate the effect of pegloticase with MTX vs. pegloticase with placebo for MTX on the mean change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) to each visit.

- Assess the PK of pegloticase.

- Assess the MTX polyglutamate concentrations.

- Assess the incidence of anti-polyethylene glycol (PEG) and anti-uricase immunoglobulin (IgG) antibodies.

3.4. Safety and Tolerability Objectives

- Evaluate the safety and tolerability of pegloticase with MTX vs. pegloticase with placebo for MTX by examining the following:

    - Adverse event (AE)/serious adverse event (SAE) profile overall for pegloticase and the combination of pegloticase and MTX

        - And in particular, the Incidence of adverse event of special interest (AESI): infusion reactions (IRs), anaphylaxis, gout flares, cardiovascular events

    - Mean change in laboratory results

    - Mean change in vital sign parameters

3.5. Brief Description

This is a Phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of pegloticase with MTX vs. pegloticase with placebo for MTX in treating adult subjects with uncontrolled gout.

The study design will include: 1) Screening Period (screening should be completed within 4-6 weeks prior to Week -6); 2) 2-week MTX Tolerability Assessment Period consisting of 2 weeks of open-label oral MTX for all subjects; 3) Run-in Period consisting of randomization followed by 4 weeks of blinded oral MTX or placebo for MTX; 4) 52-week Pegloticase + IMM Period; 5) 30-day Safety Follow-up (Phone/Email/Site Visit) and 6) 3 and 6 month Post Treatment Follow-up.

All subjects who meet eligibility criteria at Screening will begin weekly 15 mg MTX orally at the Week -6 visit. Subjects will also take folic acid 1 mg orally every day beginning during the MTX Tolerability Assessment Period (Week -6 to Week -4) and continuing until prior to the Week 52 Visit.

Subjects must be able to tolerate the weekly dose of MTX 15 mg for 2 weeks to be eligible to be randomized at Week -4. Subjects who are unable to tolerate the 15 mg dose of MTX during the 2 weeks preceding the Week -4 visit during the Run-in Period will be considered screen failures.

Subjects who tolerate the weekly 15 mg MTX dose during the 2 weeks preceding Week -4 Visit and continue to meet eligibility criteria will be randomized at the Week -4 Visit in a 2:1 ratio (stratified by presence of tophi) to receive either blinded oral 15 mg MTX or blinded oral placebo for MTX. Tophi presence (yes, no) will be based on presence of at least one tophus identified by the Investigator. Subjects will continue to take the blinded MTX or placebo for MTX from Week -4 to Day 1 (the Run-in Period) at the 15 mg MTX or placebo for MTX dose. If a subject does not tolerate the 15 mg MTX or placebo for MTX dose after randomization at the Week -4 Visit and prior to Day 1, the MTX or placebo for MTX may be dose-reduced or discontinued based on pre-specified criteria and after discussion with the Sponsor medical monitor. The subject will be allowed to remain in the study. After Day 1, MTX or placebo for MTX may be re-initiated. The subject will be re-initiated to the same treatment they were randomized to at Week -4. The re-initiated MTX or placebo for MTX will remain blinded.

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.

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 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 (180 mg orally) will be taken the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) will be taken the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, initiated immediately prior to each infusion.

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 or placebo for 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 or placebo for MTX must be taken ≥60 minutes prior to each pegloticase infusion.

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

After the Week 52 Visit (or End of Pegloticase Infusion Visit [if applicable]), subjects should resume regular care for gout per the judgment of the treating physician, including resumption of urate lowering therapy (ULT) upon pegloticase discontinuation, if appropriate. Subjects will have a 3 and 6 Month Follow-up visit to assess clinical status, including sUA levels.

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

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

An external DMC will be convened to review data for safety and efficacy with the timepoint of review and criteria outlined in the DMC Charter, with the possibility of DMC recommendation on study cessation or study design modification per criteria also to be outlined in the Charter.

An independent external adjudication committee will review reported events of infusion reactions, cardiovascular events and anaphylaxis.

3.6. Determination of Sample Size

The response rate during Month 6 on pegloticase 8 mg every 2 weeks was 43% for the phase 3 studies. A sample size of 135 subjects (90 subjects randomized to receive pegloticase with MTX, 45 subjects randomized to receive pegloticase with placebo for MTX) provides 88% power at the 2-sided alpha=0.05 level to detect a difference of 28% (71% response rate for pegloticase with MTX vs. 43% for pegloticase with placebo for MTX).

The COVID-19 pandemic outbreak occurred midway through enrollment for the study, which has affected some subject enrollment and data acquisition during the trial. As a result, the Sponsor has planned to enroll approximately 10 additional subjects (for a total of 145 randomized subjects), in order to obtain information equivalent to studying at least 135 subjects not impacted by COVID-19.

3.7. Treatment Assignment & Blinding

Pegloticase

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

Methotrexate

The Sponsor, Investigator, study site personnel and study subject will remain blinded to each subject's treatment assignment (MTX or placebo for MTX). [redacted] will provide access to blinded subject treatment information during the study in the case of medical emergency. The study blind should be broken only if the safety of a subject is at risk and the treatment plan depends on which medication (MTX or placebo for MTX) he or she received. Unless the subject is at immediate risk, the Investigator must make diligent attempts to contact the Sponsor or Sponsor's designee before unblinding the subject's study medication. If a subject's study medication is unblinded without prior knowledge of the Sponsor, the Investigator must notify the Sponsor as soon as possible and no later than the next business day. All circumstances surrounding the event must be clearly documented.

The Sponsor's Pharmacovigilance department or designee will unblind the identity of the study medication for an unexpected, drug-related SAE (related to MTX or placebo for MTX only) for submission to health authorities and IRB/IEC according to applicable regulatory requirements. However, the results will not be shared with other Sponsor representatives or staff at study sites. Details of subjects who are unblinded during the study will be included in the Clinical Study Report.

Unblinding for independent pharmacological analysis of biological samples or SAE reporting will be performed according to procedures in place to ensure integrity of the data.

The date and the reason that the blind was broken must be recorded.

Unblinding of Data for the Data Monitoring Committee (DMC)

The external DMC will oversee and interpret the interim analyses of safety and efficacy data per a pre-defined charter. The external statistical vendor will provide unblinded results for the DMC review, while maintaining the Sponsor blind.

All investigative site staff directly involved in this study will remain blinded from randomization through analysis of the final data and all site close-out visits, except for emergency unblinding as described in Section 9.4.8 in protocol. The Sponsor and its designees will remain blinded until after the database lock for the primary analysis following completion of all subjects in the Pegloticase + IMM treatment period unless directed otherwise by the DMC.

3.8. Administration of Study Medication

During the MTX Tolerability Assessment Period (Week -6 until the Week -4 visit), all subjects will take weekly open-label MTX 15 mg orally.

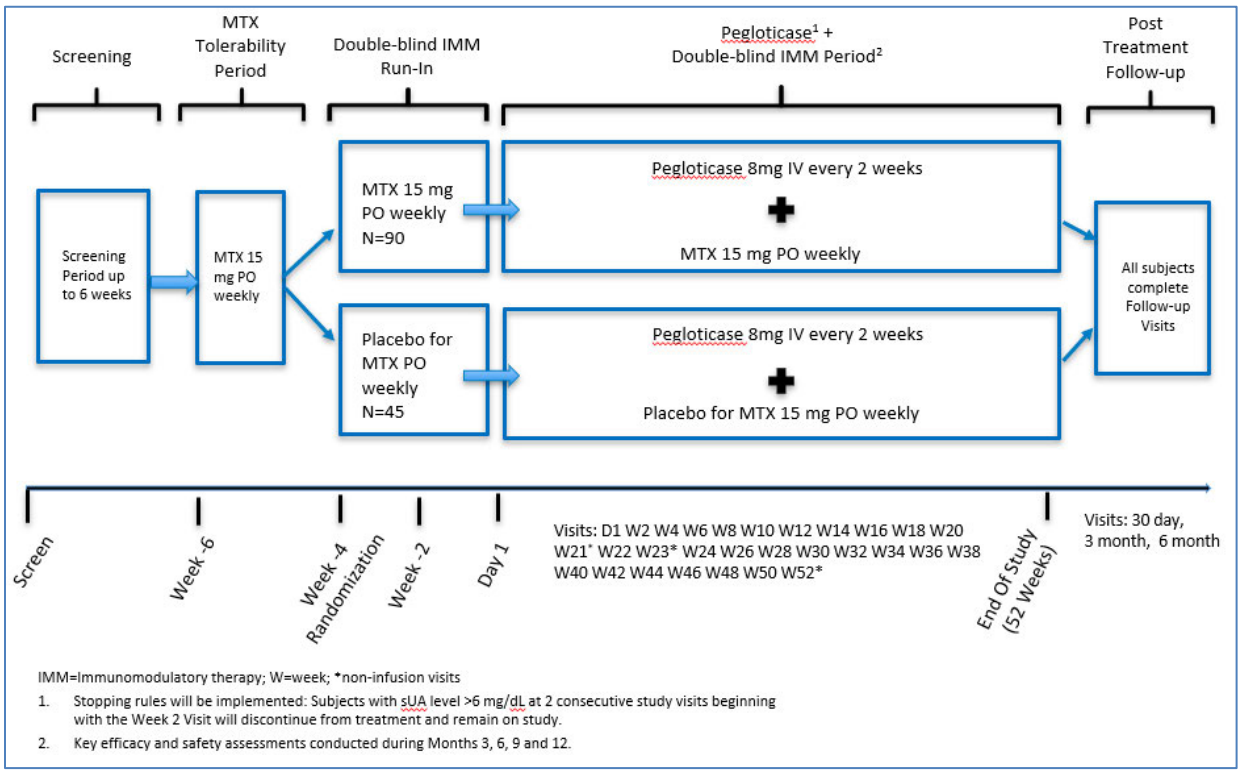
At the Week -4 visit, subjects who tolerated MTX during the tolerability period will be randomized to receive MTX 15 mg or matching placebo orally once a week from Week -4 to Day 1 (Run-in Period). During the Run-in Period, subjects will take the blinded MTX or placebo at the 15 mg dose.

During the Pegloticase + IMM Period, all subjects will receive pegloticase at a dose of 8 mg administered IV every 2 weeks for a total of 26 infusions from Day 1 through the Week 50 Visit.

Subjects will continue taking MTX or placebo 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.

3.9. Study Procedures and Flowchart

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



The schedule of assessments is copied from the protocol.

	Screening[1]	MTX Tolerability Assessment Period/ Run-in Period[2]			Pegloticase + IMM Period[3] (Day 1 through Week 24)														
	Screening Visit	(-6 wks ±3 d)	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 8 (±3 d)	Wk 10 (±3 d)	Wk 12 (±3 d)	Wk 14 (±3 d)	Wk 16 (±3 d)	Wk 18 (±3 d)	Wk 20 (±3 d)	Wk 21 (±3 d)	Wk 22 (±3 d)	Wk 23 (±3 d)	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																		
Randomization			X																
Demographic data	X																		
Inclusion/exclusion criteria	X	X	X																
Medical/surgical /substance use history[4]	X																		
Medication use history[5]	X																		
Chest X-ray[6]	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		X
Electrocardiogram[9]	X																		
AE/SAE assessment[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Document gout flares and intensity	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Swollen/tender joint counts		X			X			X				X			X				X
HAQ	X	X			X			X				X			X				X
Physician global assessment	X	X			X			X				X			X				X

	Screening[1]	MTX Tolerability Assessment Period/ Run-in Period[2]			Pegloticase + IMM Period[3] (Day 1 through Week 24)														
	Screening Visit	(-6 wks ±3 d)	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 8 (±3 d)	Wk 10 (±3 d)	Wk 12 (±3 d)	Wk 14 (±3 d)	Wk 16 (±3 d)	Wk 18 (±3 d)	Wk 20 (±3 d)	Wk 21 (±3 d)	Wk 22 (±3 d)	Wk 23 (±3 d)	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
DECT[11]					X							X							X
Digital photography[12]		X			X							X							X
X-ray of hands and feet[13]					X														X
MTX/placebo for MTX dosing calendar		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MTX/placebo for MTX dispensed[14]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MTX/placebo for MTX dosing[14]		Once weekly from Week -6 until prior to the Week 52 Visit, inclusive																	
Gout prophylaxis Rxs filled[15]		Rxs filled as needed																	
Fexofenadine Rx filled[16]		Rxs filled as needed																	
Folic acid Rx filled[17]		Rxs filled as needed																	
MTX/placebo for MTX compliance/ reconciliation			X	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Infusion reaction prophylaxis[18]					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		X
Pegloticase infusion					X	X	X	X	X	X	X	X	X	X	X		X		X
Pegloticase PK sampling[19]					X	X		X				X				X			X

	Screening[1]	MTX Tolerability Assessment Period/ Run-in Period[2]			Pegloticase + IMM Period[3] (Day 1 through Week 24)													
	Screening Visit	(-6 wks ±3 d)	(-4 wks ±3 d)	(-2 wks ±3 d)	Day 1	Wk 2 (±3 d)	Wk 4 (±3 d)	Wk 6 (±3 d)	Wk 8 (±3 d)	Wk 10 (±3 d)	Wk 12 (±3 d)	Wk 14 (±3 d)	Wk 16 (±3 d)	Wk 18 (±3 d)	Wk 20 (±3 d)	Wk 21 (±3 d)	Wk 22 (±3 d)	Wk 23 (±3 d)	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
Pre-infusion MTX Polyglutamate sampling					X							X							X
sUA[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology sample	X	X	X	X	X	X		X				X					X		X
Clinical chemistry sample	X	X	X	X	X	X		X				X					X		X
Spot urine collection					X							X							X
Antibody sample[21]					X	X		X				X					X		X
Additional samples for future analysis [22]		X			X	X	X	X	X	X	X	X							X
G6PD test	X																		
Pregnancy test[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X
PI assessment of subject clinical status and subject treatment goals[24]	X																		X
Allantoin Sample (Blood and Urine)[25]					X							X							X

	Pegloticase + IMM Period[3] (Week 26 through Week 50)													End of Pegloticase Infusions Visit[26] (if applicable)	End of Study/ Early Termin-ation	Safety Follow-up Phone/ Email Visit	MTX Partner Pregnancy Follow-up	Post Treatment Follow-up[27] (if applicable)
	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 and 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	X			X
HAQ			X			X				X				X	X			X
Physician global assessment			X			X				X				X	X			X
DECT[11]														X	X			X
Digital photography[12]						X								X	X			X
X-ray of hands and feet[13]														X	X			
MTX/placebo for MTX dosing calendar	X	X	X	X	X	X	X	X	X	X	X	X	X					
MTX/placebo for MTX dispensed[14]	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[26] (if applicable)	End of Study/ Early Termin-ation	Safety Follow-up Phone/ Email Visit	MTX Partner Pregnancy Follow-up	Post Treatment Follow-up[27] (if applicable)
	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 and 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**					
MTX/placebo for MTX dosing[14]	Once weekly from Week -6 to prior to the Week 52 Visit, inclusive																	
Gout prophylaxis Rxs filled[15]	Rxs filled as needed																	
Fexofenadine Rx filled[16]	Rxs filled as needed																	
Folic acid Rx filled[17]	Rxs filled as needed																	
MTX/placebo for MTX compliance/ reconciliation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Infusion reaction prophylaxis[18]	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	X			
Pegloticase infusion	X	X	X	X	X	X	X	X	X	X	X	X	X					
Pegloticase PK sampling[19]						X								X	X			
Pre-infusion MTX Polyglutamate sampling						X												

	Pegloticase + IMM Period[3] (Week 26 through Week 50)													End of Pegloticase Infusions Visit[26] (if applicable)	End of Study/ Early Termin-ation	Safety Follow-up Phone/ Email Visit	MTX Partner Pregnancy Follow-up	Post Treatment Follow-up[27] (if applicable)
	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 and 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**					
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 testing[21]						X								X	X			X
Additional samples for future analysis[22]						X								X	X			
Pregnancy test[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PI assessment of subject clinical status and subject treatment goals[24]														X	X			
Allantoin Sample (Blood and Urine)[25]						X								X	X			
Partner pregnancy[26]																	X	

AE = adverse event; d = day(s); Inf = infusion; DECT = dual-energy computed tomography; G6PD = glucose-6-phosphate dehydrogenase; HAQ = Health Assessment Questionnaire; 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 Visit can occur any time within 4-6 weeks prior to the first dose of MTX at Week -6.
2. During the MTX Tolerability Assessment Period (Week -6 until the Week -4 visit), all subjects will take MTX 15 mg orally weekly. At the Week -4 visit, subjects who tolerated methotrexate will be randomized to receive MTX 15 mg or placebo for MTX orally weekly. Subjects will be blinded to MTX or placebo for MTX beginning at Week -4 through

the remainder of the study. Subjects will continue to take the blinded MTX or placebo for MTX during the Run-in Period (from Week -4 to Day 1) at the 15 mg MTX dose or placebo for MTX dose. If a subject does not tolerate the 15 mg MTX or placebo for MTX dose after randomization at the Week -4 Visit and prior to Day 1, the MTX or placebo for MTX may be dose-reduced or discontinued based on pre-specified criteria and after discussion with the Sponsor medical monitor. The subject will be allowed to remain in the study.

3. 52-week Pegloticase + MTX or Pegloticase + placebo for MTX Period.
4. The Investigator or designee will collect a complete gout history and other relevant medical/surgical/substance use history.
5. Medication history will be collected at Screening. History of all prior gout medications will be collected. History of non-gout medication use in the year prior to Screening will be collected.
6. Subjects that do not have a chest X-ray within 2 years prior to Screening will have an X-ray done during Screening, if deemed necessary by the Investigator.
7. A complete physical examination will be performed at the Screening Visit, including assessment of HEENT, heart, lungs, abdomen, skin, extremities, neurological status and musculoskeletal including an assessment for the presence of tophi. A targeted physical examination per investigator judgement will be conducted at Week -6, Day 1, and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20, 24, 36 and the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and 3 and 6 month Post Treatment Follow-up Visits; at a minimum this should include heart, lungs, and abdominal exam. Clinically significant findings from the targeted physical examinations will be recorded as AEs.
8. Routine vital signs, including blood pressure, respiratory rate, temperature, and heart rate will be measured at Screening, Week -6, Week -4, Day 1 and Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 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. Heart rate and blood pressure measurements should be taken after the subject has been in a sitting position and in a rested and calm state with proper positioning including back support, feet flat on the floor, for at least 5 minutes. Subjects arm should be supported at heart level; and cuff placed on the bare arm. A large cuff should be used as needed to fit the upper arm and a consistent arm is to be used at each study visit. The Korotkoff phase V will be used to determine diastolic blood pressure. 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. At sites who participate and from subjects who consent, optional intensive BP collections will be obtained at designated timepoints. Optional intensive blood pressure measurements will be taken prior to the infusion on Day 1 and at Weeks 6, 12, 18, 24, 30, 36, 42, 48 and at the non-infusion End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visit. At these intensive blood pressure collections, three blood pressure measurements should be performed, at least 2 minutes apart, with BP readings measured to the nearest mm Hg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differed by more than 8 mm Hg or if diastolic measurements differed by more than 5 mm Hg, a separate set of 3 sitting blood pressure measurements will be obtained until the difference is less than 8 mm Hg for systolic and less than 5 mm Hg for diastolic. All values will be recorded in the eCRF. When possible, the same staff member should take all BP measurements for a given subject. Weight should be measured in kilograms or pounds without shoes and recorded at the Screening Visit and prior to dosing MTX Week -6 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.
9. Electrocardiogram should be completed during Screening. The Electrocardiogram is read at the site. When possible, a 12-lead ECG will also be performed at the time the AESI of infusion reaction, anaphylaxis and cardiovascular event is suspected.
10. AEs/SAEs will be collected from the signature of the ICF until the 6 month Post Treatment Follow-up Visit. For each AE, the Investigator will be asked to record if the event was possibly an infusion reaction or anaphylaxis and if so, will be prompted to complete additional eCRFs. Females of childbearing potential will be asked to confirm if ovulation has occurred since the last dose of MTX or placebo for MTX. If the subject had not ovulated, a urine pregnancy test will be required.

11. For sites with DECT capability and subjects who provide consent, an optional 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 and the 6 month Post Treatment Follow-up Visit for subjects that completed 52 weeks of treatment and consent to the additional assessment. The DECT on Day 1 must be completed prior to the infusion and may be completed within the 14 days prior to Day 1. The DECT at all other scheduled timepoints may be completed within +/- 10 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 (detailed guidance is provided with the imaging manual).
12. Digital photography will be completed at Week -6, Day 1 and Weeks 14, 24, 36, and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination and the 3 and 6 month Post Treatment Follow-up Visits. Digital photography of hands and feet will be performed according to the instructions provided in the digital photography manual. Other anatomical sites with large tophi may be photographed in addition to the hands and feet at the Investigator's discretion.
13. For sites with X-ray capability and subjects who provide consent, an optional X-ray of the hands and feet will be obtained at Day 1, Week 24 and End of Pegloticase Infusions Visit (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 X-ray within 3 months of a prior X-ray (detailed guidance is provided with the imaging manual). The X-ray on Day 1 must be completed prior to the infusion and may be completed within the 14 days prior to Day 1. The X-ray at all other scheduled timepoints may be completed within +/- 10 days of the scheduled timepoint.
14. MTX or placebo for MTX will be dispensed and brought back to check compliance. MTX or placebo for MTX should be taken 1 to 3 days prior to each pegloticase infusion; however, if a subject does not do so, MTX or placebo for MTX must be taken $\geqslant$60 minutes prior to each pegloticase infusion.
15. 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 $\geqslant$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.
16. For IR prophylaxis, fexofenadine (180 mg orally) will be taken the day before and the morning of just prior to each infusion.
17. Subjects will take folic acid 1 mg orally every day beginning at Week -6 (the start of MTX) until prior to the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of Study/Early Termination.
18. Infusion reaction prophylaxis includes fexofenadine (180 mg orally) administered the day before each infusion; fexofenadine (180 mg orally) and acetaminophen (1000 mg orally) administered on the morning of each infusion; and methylprednisolone (125 mg IV) given over an infusion duration between 10 - 30 minutes, immediately prior to each infusion.
19. For all subjects, serum samples for PK analysis will be collected after the end of infusion on Day 1 (prior to discharge); prior to the pegloticase infusion and after the end of infusion (prior to discharge) at the Weeks 2, 6, 14, 21, 24, 36 and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visits. NOTE: Week 21 Visit and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visits are non infusion visits.
20. Serum samples for measurement of sUA levels will be collected at the Screening Visit, the Week -6 Visit (prior to the first dose of MTX), the Week -4 Visit (Randomization) and the Week -2 Visit during the Run-in Period. On Day 1, a pre-infusion and post infusion sUA will be collected to be shipped to the Central laboratory. For the remainder of study visits beginning at Week 2 during the Pegloticase +IMM period; 2 Serum Uric Acid samples will be collected within 48 hours PRIOR to each pegloticase infusion until Week 24 visit. After Week 24, if a subject's previous visit sUA (local or central laboratory) is less than 6 mg/dl; it will be allowable to draw the local pre-infusion sUA sample on the same day and similar time as the sample to send to the central laboratory; however, if the prior visit sUA sample was greater than 6 mg/dl (local or central laboratory), a local sUA sample will need to be collected and read out prior to the pegloticase infusion to be certain the subject has not met the stopping rule. One sample will be for testing at the site's local laboratory for sUA levels and the second sample will be sent to the Central Laboratory. A POST infusion sUA blood sample will additionally be collected on Day 1, and at the Weeks 2, 6, 10, 12, 14, 20, 22, 24, 32, 34, 36, 48 and 50 for same day shipment to the Central Laboratory. Additional serum

samples for sUA levels will be collected at non-infusion Visits at Weeks 21 and 23 and the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of study/Early Termination Visit and 3 and 6 month Follow-up Visits. Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue pegloticase and complete the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of study/Early Termination Visit. See the Laboratory Manual for instructions for alternate scenarios. 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.

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, 6, 14, 22, 24, 36; and at the non-infusion End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of Study/Early Termination Visit and Month 3 Post Treatment Follow-up Visits.
22 For subjects who provide consent, optional blood samples for PBMC, RNA isolation and serum will be collected from each consenting subject prior to the first dose of MTX on -6 week, prior to the infusion at Day 1 and Weeks, 6, 14, 24, 36 and the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End-of-Study/Early Termination. During visits at Weeks 2, 4, 8, 10 and 12, optional samples will only be collected if subjects are experiencing an acute gout flare on the day of visit.
23. For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit. A urine pregnancy test will be performed 30 days after the last MTX or placebo for 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 visit it is determined that the subject has not ovulated since the last dose of MTX or placebo for MTX; a urine pregnancy test will be performed at all other indicated visits.
24. The Investigator will review the clinical status and individual subject treatment goals at Screening, Week 24, and the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of study/Early Termination Visit.
25. Blood and urine samples (for allantoin) will be collected prior to the pegloticase infusion and after the end of each pegloticase infusion prior to discharge from the site on Day 1 and at Weeks 14, 24 and 36; Additional blood and urine samples for allantoin will be collected at the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of study/Early Termination Visit. If subject consent, subject's allantoin samples will be retained for potential future analyses which may include biomarkers relevant to gout (e.g. inflammatory markers) or gout co-morbidities in response to pegloticase or other potential treatments for gout. The samples will be retained no longer than 15 years after study completion or as required by applicable law. The samples will be stored in a secured storage space with adequate measures to protect confidentiality.
26. Subjects who are non-vasectomized males will be asked 3 months after MTX or placebo for MTX discontinuation regarding partner pregnancy. This will occur at a regulatory scheduled visit or by a separate phone/email visit.
27. 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 Section 9.3.3.1.1 in protocol for details on visits and procedures.
28. All subjects will be followed for a minimum of 6 months following treatment following the end of pegloticase infusions.

4. Endpoints

4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of Month 6 (Weeks 20, 21, 22, 23, 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 (analyzed sequentially) are:

1. 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.

2. The proportion of subjects with complete resolution of ≥ 1 tophi (using digital photography) at Week 52 in subjects with tophi at baseline.

3. The mean change from baseline in HAQ-DI score at Week 52.

4. The mean change from baseline in HAQ Pain score at Week 52.

5. The mean change from baseline in HAQ Health score at Week 52.

4.3. Exploratory Endpoints

The exploratory efficacy endpoints are:

- The mean change from baseline to Weeks 14, 24, and 52 in urate deposition volume and bone erosions due to gout based on DECT.

- The mean change from baseline to Weeks 14, 24, and 52 in bone erosions due to gout based on X-rays of the hands and feet.

- The proportion of subjects with complete resolution of ≥ 1 tophi (using digital photography) at Weeks 24 and 36 in subjects with tophi at baseline.

- The mean change from baseline in tophus size (long axis measured using digital photography) to Weeks 14, 24, 36 and 52 in subjects with tophus present at baseline.

- 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 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, 21, 22, 23 and 24) combined.

- The proportion of 5 mg/dL responders during each time interval (Month 3, Month 6, Month 9 and Month 12), defined as subjects achieving and maintaining sUA <5 mg/dL for at least 80% of the time during each time interval.
- The mean change from baseline in sUA at Weeks 14, 24, 36 and 52.
- The time to first sUA > 6 mg/dL following the first infusion.
- The time to two consecutive sUA > 6 mg/dL (stopping rule) following the first infusion.
- The percentage of non-hyperuricemic (sUA < 6 mg/dL) time during Months 3, 6, 9 and 12.
- The mean change from baseline in HAQ Pain score at Weeks 14, 24, and 36.
- The mean change from baseline in HAQ Health score at Weeks 14, 24, and 36.
- The mean change from baseline in HAQ-DI score at Weeks 14, 24, and 36.
- The mean change from baseline in tender joint count (68-point scale) at Weeks 14, 24, 36 and 52.
- The mean change from baseline in swollen joint count (66-point scale) at Weeks 14, 24, 36 and 52.
- The mean change from baseline in number of tender or swollen joints at Weeks 14, 24, 36 and 52.
- The mean change from baseline in physician global assessment of gout at Weeks 14, 24, 36 and 52.
- The proportion of subjects achieving 20%, 50%, or 70% improvement based on gout chronic response criteria at Weeks 14, 24, 36 and 52.
- The mean change from baseline in SBP and DBP to each visit.

4.4. Pharmacokinetic and Anti-drug Antibody Endpoints

The PK and anti-drug antibody endpoints are:

- PK of pegloticase.
- MTX polyglutamate concentrations.
- The incidence of anti-PEG and anti-uricase IgG antibodies.

4.5. Safety and Tolerability Endpoints

Safety and tolerability endpoints are:

- Incidence of AEs/SAEs overall and potentially attributed to the combination of pegloticase and MTX
    - Incidence of AESI: IRs, anaphylaxis, gout flares, cardiovascular events
- The mean change from baseline in laboratory test results
- The mean change from baseline in vital sign parameters

5. Analysis Populations

The following analysis populations will be defined for this study:

5.1. MTX Population

The MTX population will include all subjects who take at least one dose of MTX.

The MTX population will be used for analysis of safety data during the Tolerability Assessment Period prior to randomization and the concentrations of MTX polyglutamate.

5.2. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all randomized subjects.

The ITT population will be used for efficacy analyses; subjects will be analyzed according to randomized treatment. It will be considered the primary efficacy analysis population.

5.3. Modified Intention-to-Treat Population

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

The mITT population will be used for efficacy analyses; subjects will be analyzed according to randomized treatment.

5.4. Per-protocol Population

The Per-protocol (PP) population will include all randomized subjects who receive at least 1 dose of pegloticase, are taking the 15 mg dose of MTX or placebo at the time of first pegloticase dose, and have no major protocol deviations that will challenge the validity of their data. The PP population will be used for analysis of the primary efficacy endpoint.

Major protocol deviations will be classified as exclusionary vs. non-exclusionary from the per-protocol population. Classification of exclusionary protocol deviations will occur prior to the unblinding of treatment groups after all subjects complete the Pegloticase + IMM period. Only exclusionary deviations that occurred prior to and including Week 24 will be used for classification. Exclusionary deviations include:

- Enrollment of a subject who did not satisfy the following inclusion/exclusion criteria (see Section 9.3 of the protocol):
  - Inclusion criteria #4 and #8
  - Exclusion criteria #13, #15, and #16

- Subject received treatment other than that to which he or she was randomized
- Compliance with MTX or placebo < 80% while receiving pegloticase
- Missing >20% of pegloticase infusions unless due to adverse event

- Any other deviation that has the potential to negatively impact the validity of the primary or secondary endpoints.

Compliance will be assessed based on the drug accountability data (per method defined in Section 11.1).

"Missed infusion" is defined as a subject not receiving an infusion at a scheduled visit through Week 22 (or not attending a scheduled infusion visit) prior to discontinuation of pegloticase treatment unless the reason for not receiving infusion is due to an adverse event. Subjects are allowed to discontinue pegloticase treatment for any reason and will not be excluded from the Per-Protocol population unless they miss >20% of infusions prior to the End of Pegloticase Visit for reasons other than adverse event.

Subjects with exclusionary deviations specified above that are due to COVID-19 (other than those due to suspected or confirmed infection) will be excluded from the PP Population.

5.5. Pharmacokinetic Population

The Pharmacokinetic (PK) Population will include all randomized 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 pharmacokinetic analyses of pegloticase. Subjects will be analyzed according to the treatment received. In the event a subject receives more than one treatment, the subject will be summarized by the treatment received most frequently.

5.6. Safety Population

The safety population will include all randomized subjects who take at least one dose of blinded MTX or placebo for MTX.

The safety population will be used for analysis of safety data and ADA data; subjects will be analyzed according to the treatment received. In the event a subject receives more than one treatment (i.e. receives treatment other than randomized treatment), the subject will be summarized by the treatment received most frequently.

5.7. Protocol Deviations

Protocol deviations are entered into the electronic Case Report Form (eCRF) system. Sites will be issued following specific instructions to capture missed visits, out of window visits, treatment interruptions and treatment discontinuations due to COVID-19 on the eCRF, including whether subject has suspected or confirmed COVID-19 infection, and whether the study site is open or closed. Deviations will be categorized by type and as major or minor. Deviations will be classified as occurring in the Screening, MTX Tolerability Assessment Period, Run-in Period, Pegloticase + IMM Period, or Follow-up Period.

Using the MTX and ITT populations, major deviations will be summarized by type and period of occurrence. In addition, deviations related to COVID-19 will be summarized by type and period of occurrence. A listing of all subjects with all deviations related to COVID-19 will be presented.

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 the treatment of Pegloticase + MTX, or Pegloticase + Placebo for the ITT, mITT, and PP populations. Safety summaries will be provided for the safety population. For safety summaries during the MTX Tolerability Assessment Period, the MTX population will be used. Depending on the treatment period, different columns will be presented for safety summaries:
    - single column of MTX will be presented for MTX tolerability assessment period;
    - columns of MTX or Placebo will be presented for Run-in Period;
    - columns of Pegloticase + MTX, or Pegloticase + Placebo will be presented for Pegloticase + IMM Period.
- The following labels will be used for the populations: “ITT Population”, “mITT Population”, “PP Population”, “Safety Population”, “MTX Population”, or “PK Population”. The following column labels will be used for the treatment groups: MTX, Placebo, Pegloticase + MTX, or Pegloticase + Placebo.
- 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 otherwise specified, confidence intervals (CI) will be based on 95% confidence and two-sided.
- If multiple assessments occur at a given post-baseline 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 13.

6.2. Key Definitions

6.2.1. Baseline

For assessments without a measurement taken prior to the first dose of MTX (DECT, X-ray of hands and feet, spot urine collection, and antibody sample), the baseline value will be defined as last observation prior to the first dose of pegloticase. For all other assessments, the baseline value will be defined as the last measurement taken prior to first dosing of MTX in the MTX Tolerability Assessment Period (considering unscheduled visits when available). Change from 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 MTX Study Day and the Pegloticase Study Day. The MTX Study Day will be determined relative to the first dose of MTX in the MTX Tolerability Assessment Period. The Pegloticase Study Day will be determined relative to the first infusion of pegloticase.

For both study day calculations, 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 then truncated to a complete year. 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 Tolerability Assessment Period, concomitant in the 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
    - If 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 or placebo in Run-in Period (i.e. the MTX or placebo in Run-in Period and pegloticase started in the same month), the day of the first dose date of MTX or placebo in Run-in Period will be imputed.
    - Otherwise, if the month and year match the month and the year of the first MTX dose date in MTX Tolerability Assessment Period AND match the month and the year of the first MTX dose or placebo in Run-in Period (i.e. the MTX in MTX Tolerability Assessment Period and MTX or placebo in Run-in Period started in the same month),

the day of the first dose date of MTX in MTX Tolerability Assessment Period 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 or placebo date (either in MTX Tolerability Assessment Period, or Run-in Period), then the first dose date of MTX or placebo will be imputed.
- Otherwise, the first of the month will be used.

- If the year is provided and the month and day are missing
  - If the year matches the year of the first pegloticase dose date and the year matches the year of the first MTX dose or placebo date, the month and day of the first MTX or placebo 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 or placebo date, then the first dose date of MTX or placebo will be imputed.
  - Otherwise, January 1st 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 Tolerability Assessment Period, concomitant in the Run-in Period, and concomitant in the Pegloticase + IMM Period. If the stop date is on or after the first dose date of MTX in the MTX Tolerability Assessment Period, but prior to the first dose of MTX or placebo dose date in the Run-in Period, the medication will be considered to be prior and concomitant in the MTX Tolerability Assessment Period. If the stop date is on or after the first dose date of MTX or placebo in the Run-in Period, but prior to the first dose date of pegloticase, the medication will be considered to be prior and concomitant in the MTX Tolerability Assessment Period and Run-in Period. If the stop date is prior to the first dose date of MTX in the MTX Tolerability Assessment Period, 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 Tolerability Assessment Period, 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 Tolerability Assessment Period AND match the month and year of the first MTX or placebo in the Run-in Period, the first dose date of MTX in the MTX Tolerability Assessment Period will be imputed and the event will be considered treatment emergent in the MTX Tolerability Assessment Period, and Run-in Period.
    - If the month and year match the month and year of the first dose of MTX or Placebo in the 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 or placebo in the Run-in Period will be imputed and the event will be considered treatment emergent in the 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 in the MTX Tolerability Assessment Period, the day of the first dose date of MTX in the MTX Tolerability Assessment Period will be imputed and the AE will be considered treatment-emergent in the MTX Tolerability Assessment Period.
    - Otherwise, if the month and year match the month and the year of the first dose date of MTX or placebo in the Run-in Period, the day of the first dose date of MTX or placebo in the Run-in Period will be imputed and the AE will be considered treatment-emergent in the 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, the first dose date of MTX in the MTX Tolerability Assessment, or the first dose date of MTX or placebo in the Run-in Period.
- 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 Tolerability Assessment Period AND matches the year of the first dose of MTX or placebo in the Run-in Period, the first dose date of MTX in the MTX Tolerability Assessment Period will be imputed and the event will be considered treatment emergent in the MTX Tolerability Assessment Period, and Run-in Period.

- If the year matches the year of the first dose of MTX or placebo in the Run-in Period AND matches the year of the first infusion of pegloticase in the Pegloticase + IMM Period, the first dose date of MTX or placebo in the Run-in Period will be imputed and the event will be considered treatment emergent in the 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 in the MTX Tolerability Assessment Period, the month and day of the first dose of MTX in the MTX Tolerability Assessment Period will be imputed and the AE will be considered treatment-emergent in the MTX Tolerability Assessment Period.

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

- If the start date is completely missing, the AE will be considered treatment-emergent in the Pegloticase + IMM Period, the MTX Tolerability Assessment Period, and the Run-in Period, unless the stop date is complete or provides enough partial information to rule out a treatment-emergent status in the MTX Tolerability Assessment Period, the Run-in Period or in the Pegloticase + IMM 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 Tolerability Assessment Period will be considered “related” to Methotrexate for statistical summaries. Events with missing relationship to study drug in the Run-in Period will be considered “related” to Methotrexate or placebo for statistical summaries. Events with missing relationship to study drug in the Pegloticase + IMM Period will be considered “related” to Methotrexate or placebo and “related” to pegloticase for statistical summaries.

Missing severities will be considered “severe” for statistical summaries.

6.3.3. Missing Data due to COVID-19 in sUA Responder Endpoints

In general, the estimand for this study will use the Treatment Policy Strategy for intercurrent events (ICEs), as planned during the design of this study. However, the COVID-19 pandemic was not anticipated, and the methodology will be changed for some ICEs. To make the analysis results applicable to the post-pandemic situation in which the virus is present in society but site closures (due to COVID-19) do not prevent office visits, subjects missing primary and secondary endpoint data due to site closure related to COVID-19 will have missing data addressed using the Hypothetical Strategy for ICEs. Under this strategy, partial data will be used for more efficient estimates of the analysis parameters.

The protocol deviation eCRF and disposition eCRFs will record reasons for missed visits, interruptions in study treatment, and reasons for treatment discontinuation. For deviations related to COVID-19, the study team will review before database lock and unblinding and assign a category for missing data as defined below. For analyses of response during a timepoint (Month 3, Month 6, Month 9, and Month 12), the following rules will be applied:

- Stopping rule: if a subject meets the sUA stopping rule prior to the analysis timepoint of interest and prior to any other COVID-19 impact (from categories below), the subject will be considered a non-responder for any timepoint after stopping rule was met.
- COVID-19 infection: if a subject is missing results during the timepoint due to confirmed or suspected COVID-19 infection prior to this period the subject will be considered a non-responder.
- Site closure: if a subject is ongoing in the study but the site is closed due to COVID-19 during the analysis timepoint of interest, resulting in missing data for the timepoint, then multiple imputation will be used to impute missing sUA values during the timepoint to calculate response.
- COVID-19 related: if a subject has missing data for the analysis timepoint of interest due to COVID-19 (e.g. had concerns about remaining in study due to pandemic, sheltering in place/unable to travel due to COVID-19 restrictions) then the subject will be considered a non-responder.

Details of the multiple imputation process are described in Section 9.2.2

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). 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 pegloticase 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, Table 6, Table 7, and Table 8 below. Table 1 shows windows for the gout assessments and sUA collections. Table 2 shows windows for vital sign assessments. Table 3 shows the visit windows for the clinical laboratory and ADA assessments. Table 4 shows the windows for swollen/tender joints, HAQ, and physician global assessment parameters. Table 5 shows the windows for the assessment of DECT. Table 6 shows the windows for the assessment of digital photography. Table 7 shows the visit windows for the MTX polyglutamate 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 (Gout Assessments and 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 – 144
	Week 21	148	145 – 151
	Week 22	155	152 – 158
	Week 23	162	159 – 165
	Week 24	169	166 – 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

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
	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 (Vital Signs)

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

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
	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 3: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (Laboratory and ADA 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
	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 4: Visit Windows for Assigning ET and End of Pegloticase Visits to a Scheduled Visit (Swollen/Tender Joint Counts, HAQ, Physician Global Assessments)

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase + IMM	Day 1	1	1
	Week 6	43	2 – 71
	Week 14	99	72 – 120
	Week 20	141	121 -155
	Week 24	169	156 - 190
	Week 30	211	191 – 232
	Week 36	253	233 – 281
	Week 44	309	282 – 337
	Week 52	365	≥ 338

[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 (DECT and Urinalysis)

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 – 267
	Week 52	365	≥ 268

[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 (Digital Photography for Tophi Assessment)

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 7: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (Pre-infusion MTX Polyglutamate Assessments)

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

[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, scheduled visits and mapped visits based on the visit windows will be used for summaries by visit.

6.5. Pooling of Centers

Data from all sites will be summarized together for analyses.

6.6. Subgroups

Subgroup analyses will be repeated for the primary and secondary efficacy analyses for the following subgroups:

1) Age group (<65, ≥ 65 years)
2) BMI (≤30, >30 kg/m^2)
3) Sex (female, male)
4) Presence of tophi (yes, no)
5) Race (white, other)
6) Randomization group (first 135 randomized, subjects randomized after 135th subject) [only to be used for the primary endpoint analysis]

7. Subject Disposition

A summary of subject disposition will be provided including the number of subjects screened and number of screen failures (summarized by those who received open-label MTX vs. those who did not), as well as the number of subjects in each analysis population (MTX, ITT, mITT, PP, Safety, and PK Populations). In addition, the number and percent of subjects in each of the following categories will be provided for the ITT Population by randomized treatment:

- Randomized and discontinued study prior to receiving randomized MTX or placebo
- Entered the Run-in Period (took at least one dose of MTX or placebo)
    - Discontinued from treatment in the Run-in Period
    - Discontinued from study in the Run-in Period along with reason for study discontinuation
- Entered the Pegloticase + IMM Period
    - Completed pegloticase treatment for the 52 Week Pegloticase + IMM Period
    - Completed MTX or placebo treatment for the 52 Week Pegloticase + IMM Period
    - Discontinued MTX or placebo treatment in the Pegloticase + IMM Period and completed pegloticase treatment
    - Discontinued prematurely from pegloticase treatment in the Pegloticase + IMM Period along with reason for treatment discontinuation
    - Discontinuations from pegloticase treatment in the Pegloticase + IMM Period will be further broken down by whether they occurred
        - Prior to Week 14 (Month 3) Time Point
        - Prior to Week 24 (Month 6) Time Point
        - Prior to Week 36 (Month 9) Time Point
        - Prior to Week 52 (Month 12) Time Point
    - Discontinued from pegloticase treatment in the Pegloticase + IMM Period but continued in the study
    - Discontinued prematurely from the study during the Pegloticase + IMM Period along with reason for study discontinuation
    - Completed study

Percentages will be based on the number of subjects in the ITT population. The number of subjects who discontinue treatment or study due to COVID-19 will be summarized. A separate summary will be provided of the number and percentage of subjects attending each visit using the ITT Population. Percentages will be based on the number of subjects in the population and randomized treatment as described in Section 6.1. MTX population subjects who are randomized are included in the ITT population. ITT population subjects who received an infusion of Pegloticase are also included in the mITT population.

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 MTX, ITT, mITT, and safety populations by treatment as described in Section 6.1. In addition, the demographic characteristics will be summarized for the ITT population by subgroups of the first 135 subjects randomized, and all subjects randomized after the 135th subject. The characteristics being summarized include: age, age category (< 65 years, ≥ 65 years), sex, race, ethnicity, 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, body mass index (BMI), 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, 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, minimum and maximum. For number of flares, if the result is '>X' the will 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), 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.

Weight will be converted to kilograms (kg) when reported in pounds (lbs) as follows: Weight (in kg) = weight (in lbs) * 0.4536. Height will be converted to meters (m) when reported in inches (in) as follows: Height (in m) = height (in inches) * 0.0254.

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 (e.g. impute January, 01 if only year is provided, or 01 for day if month and year is provided).

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 (e.g. impute January, 01 if only year is provided, or 01 for day if month and year is provided).

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 23.1, summarized and presented overall for the MTX and ITT Populations and by treatment as described in Section 6.1. 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 World Health Organization (WHO) Drug Global B3 September 2018 dictionary. Prior medications, concomitant medications used during the MTX Tolerability Assessment Period, concomitant medications used during the Run-in Period, concomitant medication used in the Pegloticase + IMM Period, and medications used in the Follow-up Period will be summarized by presenting the counts and percentage of subjects using medications overall for the MTX, ITT, and mITT (Follow-up Period only) Populations and treatment as described in Section 6.1. 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. Subjects will be counted only once for each medication class and each preferred drug name.

Prior and concomitant medications 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.

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

The following medications will be considered concomitant in the MTX Tolerability Assessment Period

- A medication with a start date on or after the first dose date of MTX in the MTX Tolerability Assessment Period but excluding medications with:
  - Start date on or after the first MTX or placebo date in the Run-in Period and
  - Those started more than 30 days after the last MTX dose, for subjects who did not receive MTX or placebo in the Run-in Period and 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 in the MTX Tolerability Assessment Period and match the month and year of first MTX or placebo date in the Run-in Period will be classified as being used in the MTX Tolerability Assessment Period and in the Run-in Period.

- A medication with a start date prior to the first dose date of MTX in the MTX Tolerability Assessment Period with a stop date strictly after the first dose date of MTX in the MTX Tolerability Assessment Period

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

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

- A medication with a start date on or after the first dose date of MTX or placebo in the 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 or placebo dose in the Run-in Period, 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 or placebo date in the Run-in Period and match the month and year of first Pegloticase infusion will be classified as being used in the Run-in Period and in the Pegloticase + IMM Period.

- A medication with a start date prior to the first dose date of MTX or placebo in the Run-in Period with a stop date strictly after the first dose date of MTX or placebo in the Run-in Period

- A medication with a start date prior to the first dose date of MTX or placebo in the 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 or placebo date in the Run-in Period and match the month and year of first Pegloticase infusion will be classified as being used in the Run-in Period and in the Pegloticase + IMM Period.

The following medications will be considered concomitant during the Follow-up Period

- A medication with 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.

- 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 Tolerability Assessment Period, concomitant in the Run-in Period, or concomitant in the Pegloticase + IMM Period. The summary tables will not be mutually exclusive. Missing date imputation rules are provided in Section 6.3.1.

A summary of medications used for gout treatment taken after the last dose of pegloticase will be produced for the mITT Population.

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, the Week -6 Visit (prior to the first dose of MTX), the Week -4 Visit (Randomization) and the Week -2 Visit during the Run-in Period; On Day 1, a pre-dose and post dose sUA will be collected to be shipped to the Central laboratory. For the remainder of study visits beginning at Week 2 during the Pegloticase + IMM period, 2 Serum Uric Acid samples will be collected within 48 hours PRIOR to each pegloticase infusion. One sample will be for testing at the site's local laboratory for sUA levels and the second sample will be sent to the Central Laboratory. A post-infusion sUA blood sample will additionally be collected on Day 1, and at the Weeks 2, 6, 10, 12, 14, 20, 22, 24, 32, 34, 36, 48 and 50 for same day shipment to the Central Laboratory. Additional serum samples for sUA levels are collected at non-infusion Visits at Weeks 21 and 23 and the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of study/Early Termination Visit and 3 and 6 month Follow-up Visits. Subjects with an sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue pegloticase and complete the End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of study/Early Termination Visit procedures.

- 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.

9.2. Primary Efficacy Endpoint and Analysis

This study will compare pegloticase 8 mg co-administered with MTX to pegloticase 8 mg co-administered with placebo in subjects with uncontrolled gout. The primary efficacy endpoint is the proportion of Month 6 (Weeks 20, 21, 22, 23, and 24) responders, defined as subjects achieving and maintaining sUA < 6 mg/dL for at least 80% of the time during Month 6. The objective is to demonstrate superiority of pegloticase given with MTX over pegloticase given with placebo. The primary comparison will be made for ITT population, i.e., all randomized subjects, regardless of adherence to study treatment. The comparison is between randomized (planned) treatment groups of pegloticase given with MTX over pegloticase given with placebo.

9.2.1. Calculation of Response

The sUA concentrations vs. time (collected to the nearest minute in the CRF) curve will be used to estimate the proportion of time that the sUA is < 6 mg/dl using the available pre-infusion (or values at visit when no infusion performed) and post-infusion samples with non-missing sUA values.

The Month 6 period will include pre-infusion and post-infusion results at Week 20, results at Week 21, pre-infusion and post-infusion results at Week 22, results at Week 23, and pre-infusion results at Week 24, and unscheduled assessments of sUA collected between Week 20 and Week 24

processed by the central laboratory. Results from visits where an infusion was not performed (e.g. subject discontinued pegloticase but remained in study) will be used when available. Section 9.1 shows the rules for inclusion of sUA values reported by local laboratories.

[redacted]

9.2.2. Handling of Missing Data and Multiple Imputation Process

At least two sUA observations from different visits during Month 6 must be available in order for a subject to be eligible for consideration as a responder. Subjects with only one sUA observation will be considered non-responders, regardless of the value of that single observation; subjects with no sUA values will also be considered non-responders. In addition, subjects who meet the stopping rule (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 stopping rule, as specified in Section 9.1, if both central lab and local lab sUA results are available at a visit then the central lab value will be used for stopping rule determination. For subjects with missing data due to COVID-19 that is not "Site Closure", there will be no imputation of sUA values due to missing values among those collected between Week 20 and Week 24.

For subjects with missing data due to site closure (due to COVID-19 as defined in Section 6.3.3) during Month 6 (i.e. have < 2 visits during Month 6 with sUA available), multiple imputation will be used to impute missing sUA values .

The multiple imputation process for imputing missing sUA will involve the following steps:

1) For subjects who met the stopping rule and have missing data prior to or during Month 6, last observation carried forward (LOCF) imputation will be done in order to prevent the

multiple imputation algorithm from imputing data inconsistent with known information. For example, subjects who meet the sUA stopping rule and have missing sUA after stopping rule is met would be expected to continue to have sUA > 6 mg/dL in the absence of other treatment, and thus would be expected to be non-responders. LOCF is used to provide complete data for stopping rule subjects that may be used to impute missing sUA for "Site Closure" subjects. Note that these LOCF values will only be used in the imputation model, and will be excluded from all analyses once the imputation model has been used.

2) A regression model will be created using observed data (after imputation specified in step #1 performed) from subjects not affected by site closures. A linear regression model will be fit for each sUA value comprising Month 6 (i.e., Week 20, Week 21, Week 22, Week 23, Week 24) as the dependent variable and will include independent variables of treatment group, tophi presence, sex, age, baseline weight, race (white, non-white), available pre-infusion sUA values from Day 1 up through the timepoint of each dependent variable, serious AE (yes or no), severe AE (yes or no), and number of gout flares during the Pegloticase + IMM Period up through Month 6.

3) Based on the fitted regression model, a new regression model is simulated from the posterior predictive distribution of the parameters, and the predictive mean matching method is used to impute missing values (Rubin 1987, pp. 166–167, Heitjan and Little 1991; Schenker and Taylor 1996). The predictive mean matching method imputes a value chosen randomly from a set of observed subjects with complete data (K=10) whose predicted values are closest to the predicted value for the missing entry from the simulated regression model. This will be implemented using the MI procedure in SAS with the fully conditional specification (FCS) method. Covariates will be removed from the model if the model is unable to converge due to quasi or complete separation. Missing results for covariates will be imputed using either linear regression (for continuous variables) or logistic regression or discriminant function method (for categorical variables).

4) The imputation model will be used to create 100 datasets with random number generation. These 100 datasets will include the data from subjects not impacted by COVID-19 and imputed data from subjects with "Site Closure" missing data, resulting in 100 apparently complete datasets.

5) Each subject will be classified as a responder or non-responder in each of the 100 apparently complete datasets, and the proportion of responders will be calculated for each of the 100 datasets. For subjects who meet the "Site Closure" criteria (as specified in Section 6.3.3), the imputed sUA values during Month 6 will be used to classify each subject as a responder or non-responder during Month 6. Since date and time of sUA collections during Month 6 will be missing, a duration of 7 days (168 hours) will be used for time between each visit (i.e. Week 20 to Week 21, etc.). Thus, a total time of 28 days (672 hours) during Month 6 will be used to calculate proportion of time sUA < 6 mg/dL. For all other subjects, the actual data from the study (and no imputed data) will be used to classify each subject as a responder or non-responder during Month 6.

SAS code for this analysis can be found in Appendix 19.1. Since the reason for the missing data is known to be due to the COVID-19 pandemic (documented via protocol deviation), it is reasonable to assume that the missing data is missing at random or missing completely at random (MCAR), and therefore multiple imputation is an appropriate method to use. Predictive mean

matching avoids distributional assumptions on the sUA values and avoids imputing values that are out of range (e.g., values less than 0, which cannot occur). Using multiple imputation when data are MCAR is more efficient than analyzing observed data only, due to the increased information, even though observed data would appropriately control the type I error rate and bias.

9.2.3. Analysis of the Primary Endpoint

The analysis of proportion of responders during Month 6 will use Cochran-Mantel-Haenszel (CMH) weighting to estimate the common risk difference within strata and to estimate the standard error of the common risk difference. Stratification for the analysis will use the actual stratification factor value if the subject is misclassified during the randomization. The difference in response rates, comparing pegloticase with MTX vs. pegloticase with placebo, will be estimated along with the corresponding 95% CI and p-value.

If multiple imputation is performed, this analysis will be applied to each of the 100 datasets created after the multiple imputation process specified in Section 9.2.2 has been performed. Results of the 100 analyses on apparently complete data will be pooled using Rubin's rule, resulting in a single estimate for the proportion of responders in each treatment group with two-sided 95% confidence interval, as well as the p-value comparing the randomized treatment groups and a two-sided 95% confidence interval on the difference in response rates. This will be implemented using the MIANALYZE procedure in SAS.

If multiple imputation is not performed (i.e. there are no subjects with missing data due to site closure), the proportion of responders along with a 95% confidence interval for the proportion will be summarized based on the observed data (i.e. with no imputation based on COVID-19 impact), with non-responder imputation used for subjects who meet the stopping rule or have missing results during Month 6. The proportion of sUA < 6 mg/dL responders will be plotted.

9.2.4. Supplemental Analysis of the Primary Endpoint

The proportion of time 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, 25th quartile, 75th quartile, minimum, and maximum). The number and proportion of subjects 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 primary analysis of the primary endpoint, as well as the summaries described in the previous paragraph, will be repeated for the mITT and PP populations.

For the primary endpoint analysis, subjects who meet the stopping rule (sUA values > 6 mg/dL at 2 consecutive scheduled visits excluding post-infusion values) starting at Week 2 are considered non-responders during Month 6. In practice, some physicians may choose to discontinue pegloticase if subjects have a single sUA value > 6 mg/dL. A supplemental analysis will be performed using an alternative stopping rule, in which subjects 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 methods as the primary analysis described in 9.2.1-9.2.3. This analysis

Additionally, the primary analysis will be repeated for the ITT population using a similar imputation method as described in Section 9.2.2, but imputing response status for ”Site Closure” subjects via logistic regression in the imputation model.

The multiple imputation process for imputing response (responder or non-responder) will involve the following steps:

1) Response will be calculated for all subjects except those with “Site Closure” missing data during Month 6.
2) A regression model will be created using observed data from subjects not affected by COVID-19. A logistic regression model will be fit for response status at during Month 6 as the dependent variable and will include independent variables of treatment group, tophi presence, sex, age, baseline weight, race (white, non-white), available pre-infusion sUA values from Day 1 up through Week 24, serious AE (yes or no), severe AE (yes or no), and number of gout flares during the Pegloticase + IMM Period up through Month 6.

3) Based on the fitted regression model, a new regression model is simulated from the posterior predictive distribution of the parameters. This will be implemented using the MI procedure in SAS with the fully conditional specification method. Covariates removed from the primary model (regression model in Section 9.2.2) due to quasi or complete separation will be removed from the logistic model. The augmented likelihood method will be used if maximum likelihood estimates do not exist. Missing results for covariates will be imputed using either linear regression (for continuous variables) or logistic regression or discriminant function method (for categorical variables).

4) The imputation model will be used to create 100 datasets with random number generation. These 100 datasets will include the data from subjects not impacted by COVID-19 and imputed data from subjects impacted by COVID-19, resulting in 100 apparently complete datasets.

5) The proportion of responders will be calculated for each of the 100 datasets. For subjects impacted by COVID-19 who meet the site closure criteria (as specified in Section 6.3.3), the imputed response during Month 6 will be used in calculating the proportion of responders. For all other subjects, the response based on observed sUA (and no imputed data) will be used.

SAS code for this analysis can be found in Appendix 19.1. The proportion of responders will be analyzed using the same CMH test described in Section 9.2.3.

9.2.5. Sensitivity Analysis of the Primary Endpoint

The following sensitivity analyses of the primary efficacy analysis will be performed for the ITT Population:

1) Include sUA results (if available) in the response calculation following discontinuation of treatment for subjects who meet stopping rule and continue on the study (i.e. will not automatically assign non-response if stopping rules met).
2) Exclude sUA results (treat as missing) after the start of the urate lowering therapy taken after the first dose of pegloticase if subjects receive urate lowering therapy other than pegloticase.
3) Exclude all subjects from analysis with "COVID-19 Related" or "Site Closure" (per Section 6.3.3) missing data during Month 6.
4) Impute non-response for "Site Closure" subjects in the pegloticase with MTX group and impute response for "Site Closure" subjects in the pegloticase with PBO group (i.e. a worst-case analysis).
5) If multiple imputation is performed, a tipping point analysis will be performed to evaluate the robustness of the primary analysis to the missing at random (MAR) assumptions. First, all missing data will be imputed by the FCS method described in Section 9.2.2. Then, a small adjustment value will be added to the imputed values during Month 6 for the pegloticase + MTX group in each of the 100 datasets. Response will be calculated based on the adjusted imputed sUA values for "Site Closure" subjects and observed sUA values for all other subjects, and pooled together using Rubin's rule to get a p-value. This process is repeated with a more stringent adjustment until the p-value > 0.0495.

Sensitivity analyses 1 and 2 above will be performed with the same statistical method used in primary analysis of the primary endpoint, including use of multiple imputation (if performed for primary analysis). Sensitivity analyses 3 and 4 will be performed with the same statistical method used in the primary analysis of the primary endpoint but will not apply the multiple imputation process.

As specified in Section 9.2.2, subjects are required to have at least two sUA results from different visits during Month 6 in order to be eligible for consideration as a responder. Post-hoc analysis may be performed in which this requirement is removed, and in the event that only a single sUA result is available during Month 6, response will be determined based on the value of the sUA result (e.g. if sUA < 6 mg/dL then the subject is a responder).

9.2.6. Subgroup Analysis of the Primary Endpoint

The subgroup analyses for proportion of Month 6 responders will be performed using an unstratified chi-square test within each subgroup category (Section 6.6) for the ITT population. The proportion of responders along with a 95% confidence interval for the proportion will be summarized based on the observed data (i.e. with no imputation based on "Site Closure" impact), with non-responder imputation used for subjects who meet the stopping rule or have missing results during Month 6. If there are at least 20 subjects in a subgroup category, a difference in response rates with a two-sided 95% CI, calculating using normal theory, will be reported.

9.3. Secondary Efficacy Endpoints and Analyses

9.3.1. Proportion of Month 12 Responders

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

This endpoint will be analyzed for the ITT and mITT populations.

This determination will be completed using the same linear interpolation method described for the primary efficacy endpoint in Section 9.2.1. 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 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.

If the subject's proportion of hours where sUA was less than 6 mg/dL, P, 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. A subject with the proportion of hours, P, less than 80% will be counted as non-responders.

There will be no imputation of sUA values due to missing values among those collected between Week 48 and Week 52, unless missing data is due to "Site Closure". At least two sUA observations from different visits must be available in order for a subject to be eligible for consideration as a responder. Subjects with only one sUA observation will be considered a non-responder, regardless of the value of that single observation. For subjects with "Site Closure" missing data (as defined in Section 6.3.3) during Month 12, the rules described in Section 6.3.3 will be applied. The proportion of Month 12 responders will be analyzed using the same multiple imputation method and the stratified weighting approach specified for primary analysis of the primary endpoint.

In addition, the proportion of responders along with a 95% confidence interval for the proportion will be summarized based on the observed data (i.e. with no imputation based on COVID-19 impact), with non-responder imputation used for subjects who meet the stopping rule or have missing results during Month 12 (this will be the primary analysis method if there are no "Site Closure subjects").

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, 25th quartile, 75th quartile, 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. In addition, the number and proportion of subjects with data available at Week 52 responder, data available at Week 52 non-responder (subcategories of met stopping rule at or before Week 52, did not meet stopping rule), and data not available at Week 52 non-responder (subcategories of met stopping rule at or before Week 52, missing data for other reason) will be summarized.

The proportion of sUA < 6 mg/dL responders during Month 12 will be plotted.

The subgroup analyses for proportion of Month 12 responders will be performed using an unstratified chi-square test within each subgroup category (Section 6.6) for the ITT population using same method as for the subgroup analysis of the primary endpoint. If there are at least 20 subjects in a subgroup category, a difference in response rates with a two-sided 95% CI, calculating using normal theory, will be reported.

9.3.2. Proportion of Subjects Having Tophi at Baseline with Complete Resolution of ≥ 1 Tophi at Week 52

Digital photography will be used to assess tophi. Digital photography of the hands and feet will be completed at Week -6, Day 1 and Weeks 14, 24, 36, and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination and the 3 and 6 month Post Treatment Follow-up Visits. 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 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 subject at a visit will be based upon the best response among all evaluable tophi (including measurable and unmeasured) for that subject 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 subject 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 secondary endpoint is the proportion of subjects with resolution of ≥ 1 tophi at Week 52, defined as subjects with an overall tophus response of complete response at the visit (i.e. complete response in at least one tophi and no evidence of progressive disease among other tophi).

The difference in the proportion of subjects with resolution of ≥ 1 tophi at Week 52 between pegloticase with MTX and pegloticase with placebo will be tested with a chi-square test, and the difference in rates will be estimated along with the corresponding 95% CI and p-value. The difference in the proportion of subjects with complete resolution of ≥ 1 tophi will also be summarized at Weeks 14, 24, and 36

For subjects with missing tophi results (unless missing data is due to site closure) the modified non-responder approach will be used for dealing with subjects missing tophi evaluation data at Week 52. The imputation, as described below, will be done for overall response and not at the individual tophi level.

<u>Modified non-responder imputation:</u>

- Completely missing results post-baseline – ‘Progressive Disease’ imputed as subjects’ 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.
- Photography was attempted at visit, but result was unevaluable: One-worse than the last evaluable Overall Response is imputed per Table 9.

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

Last Evaluable Overall Response	Week 52 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

Subjects with "Site Closure" missing tophus assessments for Week 52 will be excluded from analysis (i.e. will not contribute to the numerator or denominator).

In addition to the imputation methods described above, the proportion of subjects with complete response at each visit, and the number and percentage of subjects with each overall response status will be summarized as observed. That is, only subjects with evaluable results at the visit are analyzed. No imputation is done for missing or "Unable to Evaluate" Overall Response. Subjects with a missing result at each visit are not included in the denominator. The p-value for this analysis is exploratory.

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 pegloticase with MTX vs. pegloticase with placebo. This will be performed for both the imputed data and the observed data. The estimate of the common odds ratio comparing pegloticase with MTX vs. pegloticase with placebo will be provided along with the corresponding 95% CI and p-value. In addition, the p-value testing the appropriateness of the proportional odds assumption will be provided.

Additionally, the best overall response over ALL visits is defined as the best response among all tophi (including measurable and unmeasured) for that subject over *all* visits, except for Day 1 visit (e.g., if any one tophus shows complete response at a visit, the best overall response is Complete Response, even if at subsequent visits subjects may either not be evaluable or have Partial Response or Stable Disease response). If any single tophus shows progression, or if a new tophus appears during the study after Day 1 (as noticed per the particular visit evaluation in a site previously photographed), the best overall response for that subject will be Progressive Disease, regardless of the response of any other tophi. The best overall response will be analyzed using the proportional odds logistics model on both the imputed data and observed data.

The analysis described above (proportion of subjects with complete resolution , Overall Response, and Best Overall Response) will be performed for the ITT and mITT populations and will be based on available data for subjects who have baseline tophi.

Subgroup analyses for the proportion of complete resolution of ≥ 1 tophi at Week 52 will be performed for the subgroups identified in Section 6.6 (excluding tophi presence subgroup) using an unstratified chi-square test within each subgroup category for the ITT population. If there are at least 20 subjects in a subgroup category, a difference in response rates with a two-sided 95% CI, calculating using normal theory, will be reported.

9.3.3. Change from Baseline in HAQ-DI, HAQ Pain, and HAQ Health to Week 52

The HAQ including the HAQ-DI, pain and health scales, will be administered at the Screening and Week -6 (prior to the first dose of MTX) Visits; prior to pegloticase infusion at the Day 1 and Weeks 6, 14, 20, 24, 30, 36 and 44 Visits during the Pegloticase + IMM Period; and at 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.

The HAQ-DI is a self-reported functional status instrument that can be filled out by a subject in less than 5 minutes and requires 1 minute to score. The 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 inability 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].

The HAQ pain scale consists of a doubly anchored, horizontal visual analog scale (VAS), that is scored from 0 (no pain) to 100 (severe pain). Subjects are asked to rate the severity of the pain they have had because of illness in the past week by placing a vertical mark on the VAS.

The HAQ health scale consists of a doubly anchored, horizontal VAS, that is scored from 0 (very well) to 100 (very poor). Subjects are asked to rate how well they are doing, considering all the ways arthritis affects him or her, by placing a vertical mark on the VAS. In order to convert the score to a 0-100 scale, the results (in cm) in database will be divided by 15 then multiplied by 100.

For the change from baseline to Week 52 in HAQ-DI, HAQ pain score, and HAQ health score, a mixed model for repeated measures (MMRM) analysis of covariance (ANCOVA) model will be fit to the individual change from baseline value for the parameter of interest, with terms for baseline score, tophi presence at baseline, and factors of treatment group, visit, visit by treatment group interaction and visit by baseline interaction. The Post Treatment Follow-up Month 3 and Month 6 visits will not be included in the MMRM model. The unstructured (UN) variance-covariance matrix will be used. In the event that this matrix does not allow for model convergence, the following three variance-covariance matrices will be attempted in order until one converges: heterogeneous Toeplitz (TOEPH), heterogeneous compound symmetry (CSH), Toeplitz (TOEP), and compound symmetry (CS). The p-values for all terms in the model will be presented, as well as the treatment group LS means and associated SE, and their difference,

SE of the difference, 95% CIs and p-value, overall and for each visit. The p-value for the treatment difference between pegloticase with MTX vs. pegloticase with placebo at Week 52 for each HAQ parameter will be used in the sequential testing of secondary endpoints.

If there are subjects without post-baseline values (unless due to Site Closure), a change from Baseline value of 0 will be imputed at the first post-baseline visit (in order to avoid exclusion of these subjects from the MMRM analysis).

Subjects with no post-baseline HAQ assessments due to site closure will be excluded from the analysis. Otherwise, if at least one post-baseline HAQ assessment is available then "Site Closure" subjects will be included in analysis.

The primary MMRM analysis for HAQ will be performed for the ITT population and repeated in the mITT population. Subgroup analysis will be conducted for each HAQ endpoint for the ITT population using the MMRM ANCOVA model described above with an additional treatment-by-subgroup interaction term included in the model. Within each subgroup stratum, the p-values for all terms in the model will be presented, as well as the treatment group LS means and associated SE, and their difference, SE of the difference, 95% CIs and p-value.

In addition, observed values and change from 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) for the ITT population.

9.4. Exploratory Efficacy Endpoints and Analyses

All exploratory analyses will be performed on the ITT Population unless otherwise specified. For the exploratory efficacy endpoint analysis of continuous variables, a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model will be fit to the individual change from baseline value for the parameter of interest, with terms for baseline score, tophi presence at baseline, and factors of treatment group, visit, visit by treatment group interaction and visit by baseline interaction. The Post Treatment Follow-up Month 3 and Month 6 visits will not be included in the MMRM model. The unstructured (UN) variance-covariance matrix will be used. In the event that this matrix does not allow for model convergence, the following three variance-covariance matrices will be attempted in order until one converges: heterogeneous Toeplitz (TOEPH), heterogeneous compound symmetry (CSH), and Toeplitz (TOEP). The p-values for all terms in the model will be presented, as well as the treatment group LS means and associated SE, and their difference, SE of the difference, 95% CIs and p-value, overall and at each visit.

P-values for exploratory endpoints will be provided for descriptive purposes only.

No imputation of missing data will be performed for the exploratory analysis of continuous variables, as the analysis will be performed using MMRM models, which accommodate missing data and allow information from every visit to contribute to the analysis of the data. The only exception to this is that for any subject in the ITT Population without post-baseline values (unless "Site Closure"), a change from Baseline value of 0 will be imputed at the first post-baseline visit (in order to avoid exclusion from the MMRM analysis). Subjects with no post-

baseline assessments due to site closure will be excluded from analysis. Otherwise, all available data for subjects impacted by COVID-19 will be included.

For exploratory efficacy endpoint analysis of categorical variables, either CMH or chi-square test (for endpoints related to tophi) will be used.

Observed efficacy endpoints will be summarized by pegloticase treatment status (On Treatment, Post-Treatment, and Overall), visit, and treatment group. On Treatment will include post-baseline visits on or after pegloticase infusions. 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 subject completes treatment). Overall status will include all visits for all subjects regardless of pegloticase treatment status.

9.4.1. Change from Baseline in Urate Deposition Volume and Bone Erosion using DECT

For sites with DECT capability, and subjects who provide consent, an optional DECT (hands, feet, knees and other anatomical areas as clinically indicated) will be obtained at Day 1 and Weeks 14, 24 and at the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of Study/Early Termination Visit. The DECT on Day 1 must be completed prior to the infusion and may be completed within the 14 days prior to Day 1. The DECT at all other scheduled timepoints may be completed within +/- 10 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 (detailed guidance is provided with the imaging manual).

CT scans of the hands and feet have been used to assess erosive damage in the small joints of the hands and feet in rheumatoid arthritis and gout. The DECT images will be used to assess erosion change using published semiquantitative scoring systems. Erosion scoring in the hand will follow the OMERACT RAMRIS score, which assesses erosive change in 10 locations in each hand and 15 locations in each wrist. Erosive damage at each location is scored from 0 to 10, with each score representing 10% incremental loss of each carpal bone or the peripheral 1 cm of articular bone for long bones (radius, ulna, metacarpals and phalanges). The total erosion score can range from 0 to 250 for each hand. Erosion scoring in the foot will follow the method published by Dalbeth et al [4] which was based on the OMERACT RAMRIS score. Erosive damage at each location is scored from 0 to 10, as in the hand. The total erosion score can range from 0 to 70 for each foot.

The observed values and the change from baseline for urate deposition volume and bone erosion scores at each scheduled visit will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). The baseline is defined as the last non-missing measurement before the first pegloticase infusion. Changes from baseline for urate deposition volume and bone erosion score to each visit and overall will be analyzed with MMRM ANCOVA model as described in Section 9.4.

9.4.2. Change from Baseline in Bone Erosion using X-Rays

For sites with X-ray capability, and subjects who provide consent, an optional X-ray of the hands and feet will be obtained at Day 1, Week 24 and End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visit. The X-ray on Day 1 must be completed prior to the infusion and may be completed within the 14 days prior to Day 1. The X-ray at all other scheduled timepoints may be completed within +/- 10 days of the scheduled timepoint. The End of Study/ET and End of Pegloticase visits are not mapped to scheduled visits and will be summarized as separate visits.

Subjects who end pegloticase infusions prior to Week 52 should follow the scheduled timepoints but avoid a repeat X-ray within 3 months of a prior X-ray (detailed guidance is provided with the imaging manual).

The assessment of joint damage (erosion score) and its progression will use the van der Heijde modified Sharp scoring method. Bone erosions in the hands and feet will be scored in the following locations according to the following grading scheme:

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Analysis of Change from Baseline in Bone Erosion using X-Rays

The observed values and the change from baseline for bone erosion score at each scheduled visit will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). The baseline is defined as the last non-missing measurement before the first pegloticase infusion. Changes from baseline for bone erosion scores to each visit and overall will be analyzed with an MMRM ANCOVA model as described in Section 9.4.

9.4.3. Proportion of Subjects with Complete Resolution of ⩾ 1 Tophi at Weeks 24 and 36 with Tophi at Baseline

The proportion of complete resolution of ≥ 1 tophi at Weeks 24 and 36 will be calculated using the same method used for Week 52 (Section 9.3.2). The difference in the proportion of subjects with resolution of ≥ 1 tophi at Weeks 24 and 36, overall response at each visit, and best overall response between pegloticase with MTX and pegloticase with placebo will be tested with a chi-square test, and the difference in rates will be estimated along with the corresponding 95% CI and p-value.

9.4.4. Change from Baseline in Tophus Size using Digital Photography in Subjects with Tophi at Baseline

Digital photography is used to assess tophus size (long axis measured using digital photography, see Section 9.3.2) at the Week -6 (prior to the first dose of MTX) Visit during the MTX Tolerability Assessment Period; prior to pegloticase infusion at Day 1 and Weeks 14, 24, and 36, and 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 long axis will be summed over all measurable tophi at each visit. The observed values, the change from baseline, and the percentage change from baseline for the sum of the long axis at each scheduled visit will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). Only tophi that are measured at baseline and each post-baseline visit (or new tophi that appear after baseline) will be included in the analysis. If a tophus measured at baseline is unable to be evaluated at a post-baseline visit (e.g. due to poor image quality), the last available measurement (including baseline) will be carried forward in order to calculate the sum of longest diameters over all tophi. If no assessment was performed or all baseline tophi are unable to be evaluated at a post-baseline visit, tophi size will be missing for that visit. Changes from baseline for tophus size to each visit and overall will be analyzed with an MMRM ANCOVA model as described in Section 9.4.

9.4.5. Proportion of Month 9 Responders

The proportion of Month 9 (Weeks 32, 34, and 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 endpoint will be analyzed for the ITT population.

This determination will be completed using the same linear interpolation method described for the primary efficacy endpoint in Section 9.2.1. 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 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.

If the subject's proportion of hours where sUA was less than 6 mg/dL, P, is greater than or equal to 80% 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. Subjects with the proportion of hours, P, less than 80% will be counted as non-responders.

There will be no imputation of sUA values due to missing values among those collected between Week 32 and Week 36, unless missing data is due to site closure. At least two sUA observations from different visits must be available in order for a subject to be eligible for consideration as a responder. Subjects with only one sUA observation will be considered a non-responder, regardless of the value of that single observation. For subjects with "Site Closure" missing data during Month 9, the rules described in Section 6.3.3 will be applied. The proportion of Month 9 responders will be analyzed using the same multiple imputation method and the stratified weighting approach specified for primary analysis of the primary endpoint.

In addition, the proportion of responders along with a 95% confidence interval for the proportion will be summarized based on the observed data (i.e. with no imputation based on COVID-19 impact), with non-responder imputation used for subjects who meet the stopping rule or have missing results during Month 9 (this will be the primary analysis method if there are no "Site Closure subjects").

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, 25^{h} quartile, 75th quartile, 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. In addition, the number and proportion of subjects with data available at Week 36 responder, data available at Week 36 non-responder (subcategories of met stopping rule at or before Week 36, did not meet stopping rule), and data not available at Week 36 non-responder (subcategories of met stopping rule at or before Week 36, missing data for other reason) will be summarized.

The proportion of sUA < 6 mg/dL responders during Month 9 will be plotted.

9.4.6. Proportion of Month 3 Responders

The proportion of Month 3 (Weeks 10, 12, and 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 determination will be completed using the same linear interpolation method described for the primary efficacy endpoint in Section 9.2.1. 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 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 where sUA was less than 6 mg/dL, P, 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. A subject with the proportion of hours, P, less than 80% will be counted as non-responders. In addition to stopping rule, a subject who withdraws from study treatment for any reason other than the stopping rule after randomization and prior to or during Month 3 will be considered a non-responder at the time of withdrawal (and for all subsequent time points) if sUA values are not collected at the planned time points.

There will be no imputation of sUA values due to missed collections among those collected between Week 10 and Week 14, unless missing data is due to site closure. At least two sUA observations from different visits must be available in order for a subject to be eligible for consideration as a responder. Subjects with only one sUA observation will be considered a non-responder, regardless of the value of that single observation. For subjects with "Site Closure" missing data during Month 3, the rules described in Section 6.3.3 will be applied. The proportion of Month 3 responders will be analyzed using the same multiple imputation method and the stratified weighting approach specified for primary analysis of the primary endpoint.

In addition, the proportion of responders along with a 95% confidence interval for the proportion will be summarized based on the observed data (i.e. with no imputation based on COVID-19 impact), with non-responder imputation used for subjects who meet the stopping rule or have missing results during Month 3 (this will be the primary analysis method if there are no "Site Closure subjects").

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, 25th quartile, 75th quartile, minimum, and maximum). The number and proportion of subjects that discontinued treatment due to the stopping rule will be summarized. In addition, the number and proportion of subjects missing all data in analysis period, with only one measurement (above cutoff) in analysis period, and with only one measurement (below cutoff) in analysis period) will be summarized. The number and proportion of responders and non-responders will be summarized. In addition, the number and proportion of subjects with data available at Week 14 responder, data available at Week 14 non-responder (subcategories of met stopping rule at or before Week 14, did not meet stopping rule), and data not available at

Week 14 non-responder (subcategories of met stopping rule at or before Week 14, missing data for other reason) will be summarized.

The proportion of sUA < 6 mg/dL responders during Month 3 will be plotted.

9.4.7. Proportion of Overall Responders Month 3 and Month 6 Combined

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 9.2.1 for the sUA results included in Month 6. See Section 9.4.6 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	≤1	Declared Overall Non-responder
2	≤1	Any Number	Declared Overall Non-responder
3	> 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 $\mathrm{P} = 100 * \frac{\mathrm{W1+W2}}{\mathrm{T1+T2}}$

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.

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 proportion of responders during Month 3 and Month 6 combined will be analyzed using the same multiple imputation method (if performed) and the stratified weighting approach specified for primary analysis of the primary endpoint.

9.4.8. 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, Month 9, and Month 12. These will be calculated and analyzed using the same method described for the primary efficacy endpoint (Section 9.2), secondary endpoint reported in Section 9.3.1, and exploratory endpoints reported in Sections 9.4.5 and 9.4.6.

9.4.9. Change from Baseline in sUA

Observed values and change from baseline at each scheduled time point, including pre-infusion and post-infusion results for sUA will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, 25th quartile, 75th quartile, minimum, and maximum). Changes from baseline for pre-infusion sUA (or available sUA at visits with no infusion, e.g., Weeks 21 and 23) to each visit and overall will be analyzed with an MMRM ANCOVA model as described in Section 9.4.

Line plots of the observed mean pre-infusion sUA values with 95% CI at each scheduled visit will be presented using the ITT population by pegloticase treatment status (On Treatment and Overall) and treatment group. A graphical presentation of the mean pre-infusion sUA values by treatment group and Month 6 sUA responders vs. non-responders, based on the primary endpoint definition of Month 6 response, will also be produced for the ITT population.

9.4.10. Time to First sUA > 6 mg/dL Following the First Infusion

The first pegloticase infusion date will be the reference date (REFDATE). 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 central lab, or local if central is unavailable) 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 will be provided by treatment group of the 25th percentile, median, and 75th percentile. 95% CIs of the median will be provided for the median. Further, a log-rank test stratified by presence of tophi (yes, no) will be provided.

Plots of the time to first sUA > 6 mg/dL will be provided by treatment group using KM curves.

9.4.11. Time to Two consecutive sUAs > 6 mg/dL Following the First Infusion

The first pegloticase infusion date will be the reference date (REFDATE). 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 central lab, or local if central is unavailable) was > 6 mg/dL. 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. Subjects with only a single elevated pre-infusion sUA and no subsequent sUA results available will be considered to have the event. Kaplan-Meier estimates will be provided by treatment group of the 25th percentile, median, and 75th percentile. 95% CIs of the median will be provided. Further, a log-rank test stratified by presence of tophi (yes, no) will be provided.

Plots of the time to two consecutive sUA > 6 mg/dL will be provided by treatment group using KM curve.

9.4.12. Percentage of Non-Hyperuricemic (sUA < 6 mg/dL) Time during Months 3, 6, 9 and 12

The proportion or percentage of time $P = 100 * \frac{W1}{T1}$ of non-hyperuricemic (sUA < 6 mg.dL) during Months 3, 6, 9, and 12 are defined in Section 9.4.5, Section 9.2, Section 9.3.1, and Section 9.3.2.

The proportion or percentage of time during the month 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 proportion or percentage of hours will be analyzed with an MMRM ANCOVA model as described in Section 9.4.

9.4.13. Change from Baseline in HAQ-DI, HAQ Pain, and HAQ Health to Weeks 24 and 36

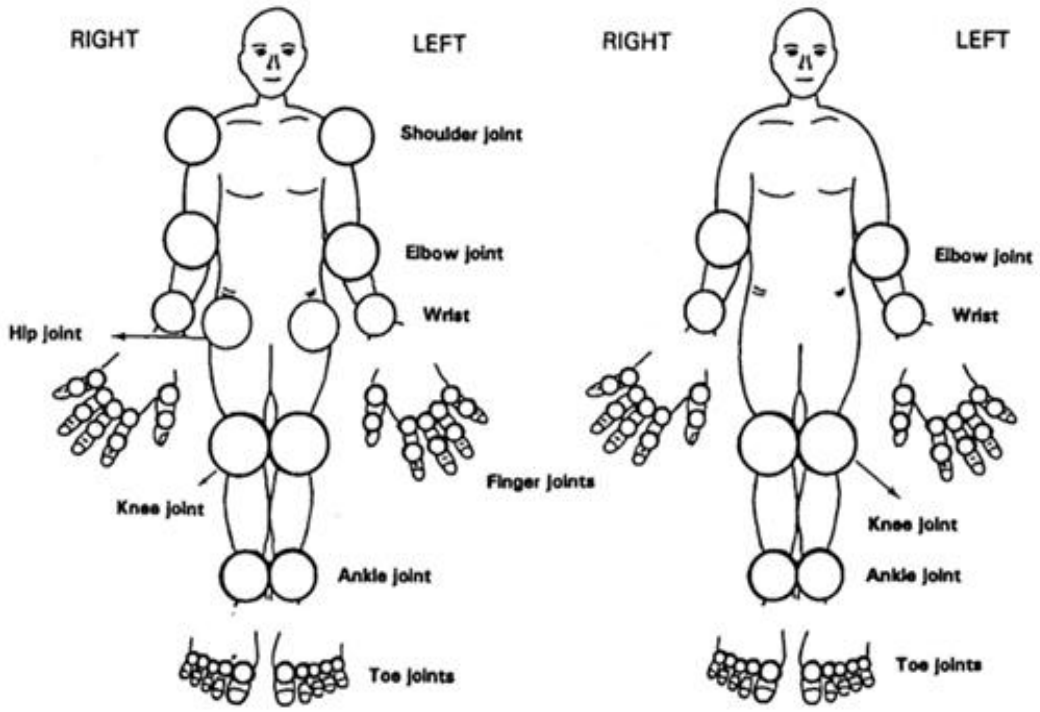
The analysis of the change from baseline in HAQ scores to Weeks 24 and 36 are described in Section 9.3.3.

9.4.14. Change from Baseline in Tender Joint Count and Swollen Joint Count

Tender and swollen (excludes hip) joint counts will be recorded at the Week -6 (prior to the first dose of MTX); prior to pegloticase infusion at the Day 1 and Weeks 6, 14, 20, 24, 36, and 44 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 shown in the Figure 1 below. All information will be entered into the appropriate eCRF.

Figure 1 Rheumatoid Arthritis 66-68 Tender and Swollen Joint Counts



For tender joint count, 68 joints are assessed as tender or non-tender (1=tender, 0=non-tender), and the tender joint count is the sum of 0s and 1s over all 68 joints for each subject. For swollen joint count, 66 joints are assessed as either swollen or non-swollen (1=swollen, 0=non-swollen) and the swollen joint count is the sum over all 66 for each subject.

Observed values, change from 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). Changes from baseline for these parameters to each visit and overall will be analyzed with an MMRM ANCOVA model as described in Section 9.4.

9.4.15. Change from Baseline in Number of Tender Joints or Swollen Joints

The number of joints (via Tender and Swollen Joint Counts assessment eCRF) are scheduled to be assessed at Screening, Weeks 6, 14, 20, 24, 36, 44 and Week 52/End of Study/Early Termination Visit, Post-treatment Follow-up Month 3, and Post-treatment Follow-up Month 6.

Observed values and change from baseline in the number of joints identified as tender or swollen at each scheduled visit will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). Changes from baseline for the number of joints to each visit and overall will be analyzed with an MMRM ANCOVA model as described in Section 9.4.

9.4.16. Change from Baseline in Physician Global Assessment of Gout

The physician global assessment will be collected at the Screening and Week -6 (prior to the first dose of MTX) Visits; prior to pegloticase infusion at the Day 1 and Weeks 6, 14, 20, 24, 30, 36, and 44 Visits during the Pegloticase + IMM Period; at the End of Pegloticase Infusions Visit (if

applicable), and the Week 52/End of Study/Early Termination Visit. The global assessment asks the physician to respond to the statement, "Considering the subject's overall health related to gout, rate their gout overall" using a numeric rating scale ranging from 0 (excellent) to 10 (very poor).

Observed values, change from baseline in the physician global assessment at selected scheduled time point will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). Changes from baseline for the physician global assessment to each visit and overall will be analyzed with an MMRM ANCOVA model as described in Section 9.4.

9.4.17. 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

The GCR response will be determined at 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 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 addition, if a subject has value of zero at baseline and also value of zero at the given post baseline for any tests above, the subject is considered to have at least 20%, 50%, and 70% reduction from the baseline for that assessment.

In the other cases, including subjects with fewer than 4 of the criteria 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.

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 and the difference between treatment groups will be analyzed using the same stratified weighting approach specified for primary analysis.

Considering some subjects also have tophus area at baseline, another analysis with the same CMH test is proposed. 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 baseline (including subjects who have zero value at baseline and zero at the given post baseline in 4 or more of the measures noted above including tophus area).

9.4.18. Change from Baseline in SBP and DBP

Routine vital signs, including blood pressure, respiratory rate, temperature, and heart rate will be measured at Screening, Week -6, Week -4, Day 1 and Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 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. Elevated levels of sUA are associated with an increased risk of hypertension [Johnson et al, 2109], so reducing sUA levels may decrease SBP and DBP over time.

Observed values and change from baseline in SBP and DBP at each scheduled time point will be summarized using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). Changes from baseline for SBP and DBP to each visit and overall will be analyzed with a MMRM ANCOVA model as described in Section 9.4.

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
- 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

The responses to the questions will be summarized descriptively by visit. The number of symptoms seeking to improve will be summarized with descriptive statistics. The clinical status assessment will be presented in a listing.

10. Analysis of Anti-Drug Antibodies and Pharmacokinetics

10.1. Anti-Drug Antibodies

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, 6, 14, 22, 24, 36, and at the non-infusion End of Pegloticase Infusions Visit (if applicable) or the Week 52/End of Study/Early Termination Visit and Month 3 Post Treatment Follow-up Visits.

Using the Safety Population for anti-PEG IgG antibodies, the number and percentage of subjects ADA positive and ADA negative at baseline will be summarized. Additionally, the number and percentage of subjects who meet the following criteria will be summarized by scheduled timepoint and treatment group:

- ADA positive in subjects ADA negative at baseline or with increase in titer from baseline,
- ADA positive in subjects ADA negative at baseline, and
- ADA positive in subjects with increase in titer from baseline

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

Kaplan-Meier estimates of the time to positive anti-PEG response (for subjects who were negative at baseline) or increase in anti-PEG titer (for subjects who were positive at baseline), and the time to anti-uricase response with 25th percentile, median, 75th percentile, and 95% CI, along with a Kaplan-Meier curve will be produced by treatment group. Subjects who never have a positive anti-PEG response or increase in titer will be censored at the date of their last visit (Week 52/End of Study/ET visit, or, if the subject did not attend this visit, then whatever last visit they have on record).

Anti-PEG and anti-uricase titer will be summarized descriptively with mean and CV% by study visit.

10.2. Pegloticase and MTX PK

For all subjects, serum samples for PK analysis of pegloticase will be collected after the end of infusion on Day 1 (prior to discharge); prior to the pegloticase infusion and after the end of infusion (prior to discharge) at the Weeks 2, 6, 14, 21, 24, 36, End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visits. NOTE: Week 21 Visit and the End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visits are non-infusion visits.

Blood samples for MTX polyglutamate analysis will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 14, 24 and 36 Visits during the Pegloticase + IMM Period .

The following presentations of subject pegloticase and MTX polyglutamate concentration data covered in this SAP will be provided:

- 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 pegloticase and MTX polyglutamate concentrations at each time point (n; mean, SD, coefficient of variation (CV)% calculated as 100% × SD/mean, minimum, 25th percentile, median, 75^{h} percentile and maximum) for the PK Population or MTX Population, respectively.

Concentrations below the limit of quantification (BLQ) collected on Day 1 pre-dose will be summarized as zero. For the summary of pegloticase concentrations, all other concentrations BLQ will be imputed as half of the lower limit of quantification value. For the summary of MTX polyglutamate concentrations, all post-baseline concentrations BLQ will be excluded from analysis. The number of BLQ values will be presented for pegloticase and MTX summaries.

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

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 Population overall and by Month 6 sUA responders and non-responders. The mean PG3 and PG3-5 concentrations over time, by Month 6 sUA responder subgroup will be plotted.

11. Safety

Safety analyses will be based on the safety population and the MTX population, depending on the treatment period. The MTX population will be used for analysis of safety data during the MTX Tolerability period prior to randomization and the safety population will be used for analysis thereafter. For summaries by study period, the number of subjects included in the Safety Population for each period will be the number of subjects with data in that period (e.g. for the Pegloticase + IMM Period, subjects must have received pegloticase).

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

All safety information will be provided in subject listings.

11.1. Extent of Exposure

Study drug exposure will be summarized from the MTX and placebo dosing calendar using the duration of treatment (in days), number of infusions, total dosage (mg) received for MTX or placebo and pegloticase, average dose (mg) received for MTX during MTX Tolerability, Run-in, and Pegloticase + IMM Period, average dose (mg) for placebo during Run-in and Pegloticase + IMM Period, and total dosage (mg) per dose overall. The MTX (or placebo) is supposed to be taken once weekly. The sequential dose number of MTX or placebo is defined by 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 subjects and percentage with compliance < 80% and ≥ 80%, in addition to being provided in listings. Interruptions in pegloticase infusions will be summarized. Reasons for infusion interruptions will be provided in the listings.

For the MTX Tolerability Assessment Period, the following will be summarized for the MTX population:

- Duration of treatment defined as (the last dose of MTX prior to the Week -4 visit date – first dose date of MTX in the MTX Tolerability Assessment Period) + 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 Tolerability Assessment Period, inclusive (in mg) (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)

- Average MTX dose (mg) (total dosage for MTX Tolerability Period divided by number of doses taken during MTX Tolerability Period) (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)

For the Run-in Period, the following will be summarized by treatment group for the Safety population:

- Duration of treatment defined as [the last dose of MTX or placebo prior to the Day 1 visit date – first dose date of MTX or placebo in the Run-in Period (Week -4)] + 1 (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)

- Total MTX or placebo dosage taken between the first and last dose dates in the Run-in Period, inclusive (in mg) (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)

- Average MTX or placebo dose (mg) (total dosage for Run-in Period divided by number of doses taken during Run-in Period) (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)

- Number of subjects with dosage reductions (reduction in planned dose for reason of AE, abnormal labs, or titration down) from planned 15 mg/week.

For the Pegloticase + IMM Period, the following will be summarized by treatment group for the Safety Population:

- Pegloticase

    - Number of pegloticase infusions received overall per subject (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 not receiving MTX or placebo between previous infusion and current infusion (for subjects infused at current 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 or placebo

- Duration of MTX or placebo dosing during the Pegloticase + IMM Period, defined as [the last MTX or placebo date – first MTX or placebo dosing date (on or after the date of the Day 1 visit)] + 1
- Cumulative MTX or placebo dosage (in mg) received during the Pegloticase + IMM period
- Average MTX or placebo dose (mg) (total dosage for Pegloticase + IMM Period divided by number of doses taken during Pegloticase + IMM Period) (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)
- Number of subjects with dosage reductions (reduction in planned dose for reason of AE, abnormal labs, or titration down) from planned 15 mg/week.

For the overall study, the following will be summarized by treatment group:

- 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
  - Average MTX or placebo dose (mg) (total dosage overall divided by number of doses taken overall) (summarized with descriptive statistics of mean, SD, median, minimum, and maximum)
  - Number of subjects with MTX dosage reductions (reduction in planned dose for reason of AE, abnormal labs, or titration down) from planned 15 mg/week.
  - Total MTX or placebo dosage (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.

Compliance with MTX or placebo 15 mg will be summarized based on drug accountability data for the Safety Population for the duration of the study after randomization. Compliance will be calculated as 100 x (the number of capsules taken divided by the expected number of capsules). Subjects 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 from the blinded bottles (i.e. excluding open label MTX given during MTX Tolerability Period). If a bottle is not returned, it will be assumed that the subject took all pills in the bottle and the number of capsules returned is set to 0. The expected number of capsules is defined as:

- 6 x [# of weeks between Week -4 visit date and the last infusion date] . For subjects who complete pegloticase infusions through the end of the study, 6 will be added to the expected number of capsules (since subjects expected to take additional MTX/PBO dose after last infusion).

The # of weeks will be calculated as [(end date – start date + 7) / 7], dates for prescribed dose are based on the MTX/PBO diary data.

Additionally, compliance with MTX or placebo during the Pegloticase + IMM period will be calculated from the MTX/PBO calendar log (a dosing dairy where subjects recorded date, time and # of capsules taken each week). Compliance based on diary data is defined as 100 x (number of MTX or placebo doses taken divided by the number of expected doses). The number of MTX or placebo doses taken will be calculated by taking the number of MTX or placebo 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 subjects should take 2 MTX or placebo doses in between each infusion).

11.3. Adverse Events

All adverse events will be coded using MedDRA version 23.1. AE monitoring will begin from the signature of the Informed Consent Form (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 Tolerability Assessment Period will be called non-treatment-emergent events.

Treatment-emergent AEs (TEAEs) for the MTX Tolerability Assessment Period are defined as events with an onset date on or after the first dose of MTX (but not on or after the first MTX or placebo date in subjects who entered the Run-in Period) through 30 days after the last dose of MTX for subjects who did not receive MTX or placebo in Run-in Period.

Treatment-emergent AEs (TEAEs) for the Run-in period are defined as events with an onset date and time on or after the first dose of MTX or placebo in the Run-in Period (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 or placebo 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 and time of the first pegloticase infusion through 30 days after the last dose of pegloticase and/or MTX or placebo (whichever is later).

Adverse events with an onset date more than 30 days after the last dose of pegloticase and/or MTX or placebo (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 Tolerability Assessment Period will be provided using the MTX Population. Summaries of TEAEs in the Run-in Period and in the Pegloticase + IMM Period will be provided for the safety population.

An overall summary of TEAEs will be provided for the MTX Tolerability Assessment Period. TEAEs will be presented by treatment group for the Run-in Period and Pegloticase + IMM Period. Summaries will include 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 or placebo
- TEAEs related to pegloticase (applicable to Pegloticase + IMM Period only)
- Serious TEAEs related to MTX or placebo
- 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 or placebo
- TEAEs leading to permanent withdrawal of pegloticase (applicable to Pegloticase + IMM Period only)
- TEAEs related to MTX or placebo leading to permanent withdrawal of MTX or placebo
- TEAEs related to pegloticase leading to permanent withdrawal of pegloticase (applicable to Pegloticase + IMM Period only)
- TEAEs leading to death

For Pegloticase + IMM Period, the number and percentage of subjects as well as the number of events with any infusion reactions including/excluding anaphylaxis will be included in the summary. In addition, the overall summary of TEAEs during the Pegloticase + IMM Period based on subgroup will be provided.

Using the safety 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 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 Tolerability Assessment Period, Run-in Period, Pegloticase + IMM Period, and Follow-up Period

- TEAEs by maximum severity, overall and by SOC and PT for the MTX Tolerability Assessment Period, Run-in Period, and Pegloticase + IMM Period

- TEAEs related to MTX or placebo overall and by SOC and PT for the MTX Tolerability Assessment Period, 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 or placebo by maximum severity, overall and by SOC and PT for the: MTX Tolerability Assessment Period, 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 Tolerability Assessment Period, Run-in Period, Pegloticase + IMM Period, and Follow-up Period

- TEAEs leading to permanent withdrawal of MTX or placebo, overall and by SOC and PT for the: MTX Tolerability Assessment Period, 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

- COVID-19 Infection TEAEs by maximum severity, overall and by SOC and PT for the: MTX Tolerability Assessment Period, Run-in Period, Pegloticase + IMM Period, and Follow-up Period

In addition, the summary of TEAEs by SOC and PT during the Pegloticase + IMM Period based on subgroup will be provided. Also, AEs that occur after the start of commercial pegloticase will be summarized by SOC and PT and relationship to commercial pegloticase for subjects who take commercial pegloticase after discontinuation of study pegloticase. Similarly, AEs that occur after the start of commercial MTX will be summarized by SOC and PT and relationship to commercial MTX for subjects who take commercial pegloticase after discontinuation of study MTX. The tables summarizing commercial product use will only be created if at least 25 subjects take commercial product.

The incidence per person years of exposure to MTX or placebo 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. The person years (PY) of exposure is defined as [(last treatment date in the period – first treatment date in the period + 1)/365.25]. Total PY of exposure to pegloticase will be calculated separately for each treatment arm.

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 or placebo, AEs leading to withdrawal of pegloticase, AEs leading to study discontinuation, AEs of special interest, COVID-19 AEs, AEs occurring while taking commercial pegloticase and/or MTX, adjudicated AEs, 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 (AESI) will include: IRs, anaphylaxis, gout flares, and cardiovascular events. All adverse events of special of interest will be summarized using MTX population for MTX Tolerability Period and Safety population for Run-in and Pegloticase + IMM Period, adjudicated as well as any identified by programming. IRs and anaphylaxis will be summarized in Pegloticase + IMM Period only. An independent external adjudication committee will review reported events of infusion reactions, cardiovascular events and anaphylaxis. The AESI of gout flare will not be adjudicated.

When possible, a 12-lead ECG will be performed at the time the AESI of infusion reaction, anaphylaxis and cardiovascular event is suspected

Infusion Reactions (IR) and Anaphylaxis

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

Examples of AEs not considered possible IRs include, but are not limited to: laboratory abnormalities that are unlikely to have occurred during or within 2 hour following the infusion (e.g., anemia), gout flares, most infectious diseases, or the recurrence or worsening of a known chronic medical problem identified in the subject's medical history.

The signs and symptoms associated with each event are entered on the eCRF and will be coded with the MedDRA dictionary.

Anaphylaxis

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives; pruritus or flushing; urticaria, and angioedema (of lips, tongue, or uvula) and ≥1 of the following:

a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue, uvula)

    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

    c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

    d. Persistent gastrointestinal symptoms (e.g., crampy, abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours): systolic blood pressure <90 millimeters mercury (mmHg) or >30% decrease from that subject's baseline.

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

- anaphylaxis
- infusion reactions including anaphylaxis
- infusion reactions excluding anaphylaxis

Both the investigator reported and adjudicated events and the associated signs and symptoms, will be summarized separately by SOC, PT, 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. Serious events and the associated symptoms will be summarized by SOC and PT. The number of events per subject, the number of events and serious events per infusion, and the number of subjects with the first event by infusion number will be summarized as well for each category. IRs (including anaphylaxis) that occur on the same date will be considered one event.

In addition, the number and percentage of subjects with adjudicated 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:

- ADA status at baseline (positive or negative)
- ADA status post-baseline (positive or negative):
    - ADA positive during treatment is defined as
        - Negative at baseline and positive at any post-baseline timepoint, or

        - Positive at baseline and had an increase in titer
    - ADA negative post-baseline is defined as
        - Negative at all time points
        - Positive at baseline, but titer did not increase from baseline

Time to first infusion reaction or anaphylaxis (Kaplan-Meier analysis) will be plotted. Time to first infusion reaction or anaphylaxis for subjects who experience infusion reaction or anaphylaxis (continuous variable descriptive stats) will be summarized. Subjects who do not experience an event will be censored at the date of their last pegloticase infusion.

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. Following search algorithm will be used to identify possible MACE:

- For cardiovascular death (for fatal cases only):
    - Standardized MedDRA Queries (SMQ): Myocardial infarction, Ischaemic Central Nervous System (CNS) Vascular conditions (narrow); Haemorrhagic central nervous system vascular conditions (narrow), Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (narrow), Embolic and thrombotic events (arterial, venous, vessel type unspecified and mixed arterial and venous) (narrow), Cardiac failure (broad), shock-associated conditions (narrow), Torsade de pointes/QT prolongation (narrow), Arrhythmia related investigations, signs and symptoms, Cardiomyopathy, 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
- For non-fatal stroke: SMQ: Ischaemic Central Nervous System (CNS) Vascular conditions; Haemorrhagic central nervous system vascular conditions; Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic
- Congestive heart failure: SMQ Cardiac failure

Using the safety population, the cardiovascular events identified using the aforementioned criteria and the adjudicated cardiovascular events will be summarized by SOC and PT for the Run-in Period and 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 Tolerability Assessment

Period using the MTX population. The number and percentage of subjects who experienced a gout flare and number of gout flares per subject during the Run-in Period and pegloticase + IMM Period (recorded in the AE eCRF) will be provided for the safety population. These events will be further summarized by month of occurrence. For the full pegloticase + IMM period, percentages will be calculated using the number of subjects in the safety population. For month 1, percentages will be based on the number of subjects in the safety population. For the other months of the pegloticase + IMM period, percentages will be based on the number of subjects who had follow-up at least through the start point of the period-specific time period. The 30 days following the end of treatment are included in the follow-up time period. For example, to be included in the Month 2 denominator, the subjects need to have received pegloticase, methotrexate, or placebo with the study day relative to the first pegloticase infusion ≥ 31 days. One month is defined as 30 days. Incidence of gout flares by severity will be summarized overall and by month. 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. Events are summarized for each period according to the onset date of the flare, and only summarized in the period of onset.

11.4. Laboratory Evaluations

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

Blood and urine samples (for allantoin) will be collected prior to the pegloticase infusion and after the end of each pegloticase infusion prior to discharge from the site on Day 1 and at Weeks 14 and 36; Additional blood and urine samples for allantoin will be collected at the End of Pegloticase Infusions Visit (if applicable) and the Week 52/End of study/Early Termination Visit.

Urine (for albumin:creatinine ratio) samples will be collected prior to the pegloticase infusion on Day 1 and at the Weeks 14, 24, 36 and the non-infusion End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visits.

Urine (for human chorionic gonadotropin) samples will be collected at all visits except the Screening Visit and Weeks 21, 23 and 3 and 6 month Post Treatment Follow-up Visits for all female subjects of childbearing potential.

Safety laboratory assessments will include:

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

- Chemistry: albumin, transaminases (aspartate aminotransferase, alanine aminotransferase), alkaline phosphatase, total bilirubin, creatinine (including calculation for Estimated Glomerular Filtration Rate (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) study equation : 175 x $(S_{cr[mg/dL]})^{-1.154}$ x $(age)^{-0.203}$x (0.742 if female) x (1.212 if African American) or 175 x $(S_{cr[\mu mol/L]}/88.4)^{-1.154}$ x $(age)^{-0.203}$x (0.742 if female) x

(1.212 if African American), glucose, sodium, potassium, calcium, chloride, total protein, blood urea nitrogen, and human chorionic gonadotropin (at the Screening Visit for all female subjects of childbearing potential)

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

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

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 baseline will be summarized by pegloticase treatment status (On Treatment, Post-Treatment, and Overall, see Section 9.4), visit, and treatment group for the safety 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 safety population , shift tables using categories of low, normal, and high, comparing laboratory test results from 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:

- 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. Laboratory results as well as results out of normal range will be presented in listings.

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 -6, Week -4, Day 1 and Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 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.

At sites who participate and from subjects who consent, optional intensive blood pressure measurements will be taken prior to the infusion on Day 1 and at Weeks 6, 12, 18, 24, 30, 36, 42, 48 and at the non-infusion End of Pegloticase Infusions Visit (if applicable) and Week 52/End of Study/Early Termination Visit. At these intensive blood pressure collections, three blood pressure measurements should be performed, at least 2 minutes apart, with blood pressure readings measured to the nearest mmHg prior to pegloticase infusion. If any of the 3 systolic blood pressure measurements differ by more than 8 mmHg or if diastolic measurements differ by more than 5 mmHg, a repeat sets of 3 sitting blood pressure measurements will be obtained until the difference is less than 8 mmHg for systolic and less than 5 mmHg for diastolic. All values will be recorded in the eCRF. Additional sets of 3 measurement may be taken until none of the 3 systolic measurements differ by 8 mmHg and none of the 3 diastolic measurements differ by more than 5 mmHg. The average of the 3 values will be used in the summary. If more than 1 set of measurements is taken, the set of measurements performed last will be used for the pre-infusion timepoint at a visit.

Weight should be measured in kilograms or pounds without shoes and recorded at the Screening Visit and prior to dosing MTX Week -6 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. BMI will be determined using the weight recorded in kg and the height measured at screening.

Descriptive summaries of observed and change from baseline values will be presented for each vital sign parameter by pegloticase treatment status (On Treatment, Post-Treatment, and Overall, see Section 9.4), and visit, using the safety population. 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)^2;

11.7. Electrocardiograms

A 12-lead ECG will be performed at Screening 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 safety population, a summary will be provided of subjects at Screening (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-Screening ECGs are done at the discretion of the investigators, or in the event of an infusion reaction, only the following summaries will be provided using the safety population:

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

For the post-Screening ECG summary, percentages will be calculated using the number of subjects who have a post-Screening assessment.

11.8. Physical Examination

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

A targeted physical examination per investigator judgement will be conducted at Week -6, Day 1, and prior to administration of pegloticase at Weeks 4, 8, 12, 16, 20, 24, 36 and the non-infusion End of Pegloticase Infusions Visit (if applicable), Week 52/End of Study/Early Termination and 3 and 6 month Post Treatment Follow-up Visits; at a minimum this should include heart, lungs, and abdominal exam.

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

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

12. Changes from Analysis Planned in Protocol

In those cases in which this SAP details changes from the analyses specified by the protocol, the analyses specified in this SAP will supersede those in the protocol. There are no changes from Amendment 3 of the protocol but details and clarifications are described in this SAP.

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.
- Title case or 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.
- Tables, Figures and Listings (TLFs) 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 TLFs, 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 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., cm^2, C_{max}) will be employed on a case-by-case basis.
- Title case of 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-202

- All output should have Page n of N at the top or bottom right corner of each page. TLFs 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) will be used to identify TLFs 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 will 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 inclusion based on the treatment(s) received: Screen Failure vs. Screen Failure, received MTX vs. Pegloticase with MTX or Pegloticase with Placebo for MTX, subject number, visit/collection date, 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 Syneos Health Standard Operating Procedure (SOP) Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) 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.

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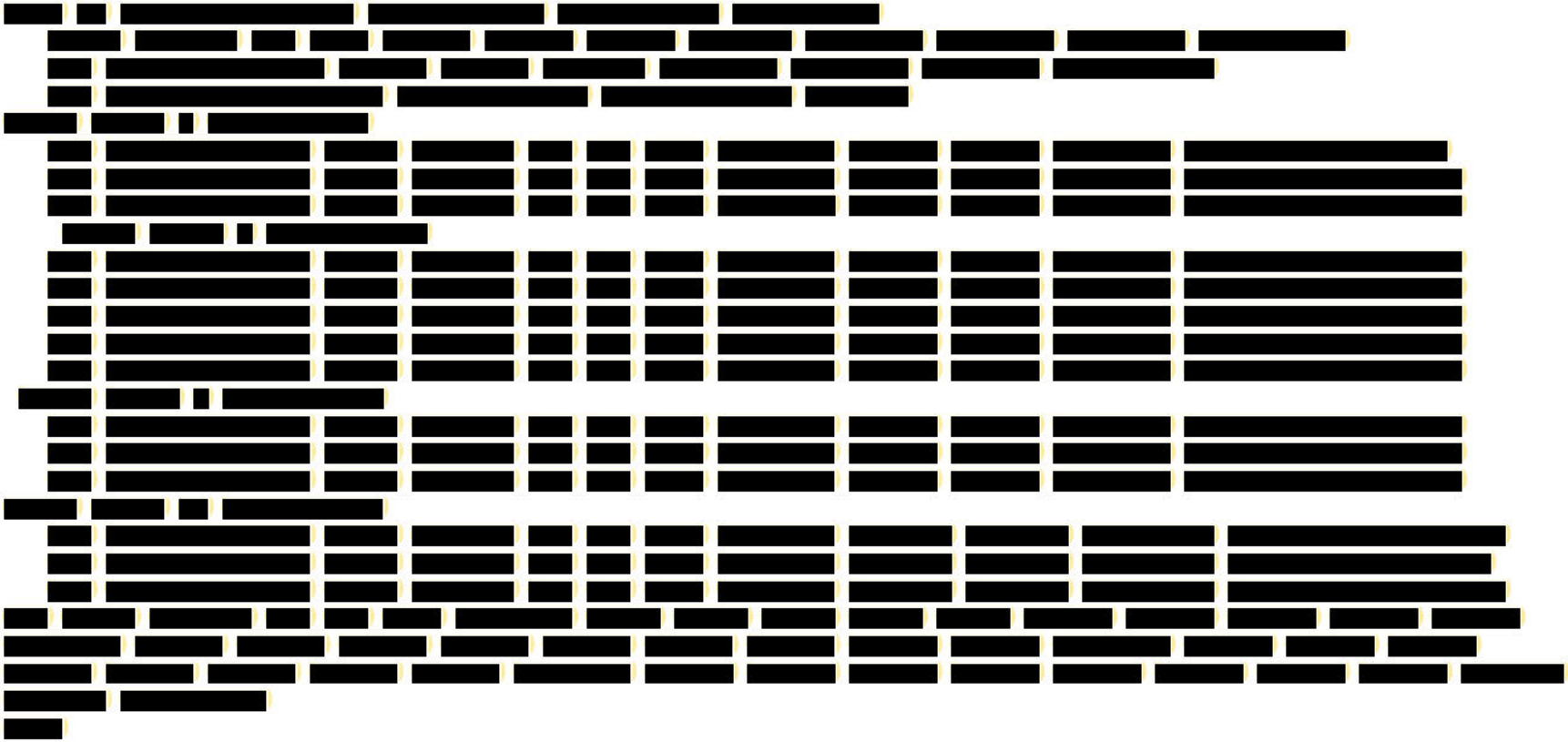
Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

19. Appendix – SAS Code

19.1. Multiple Imputation

Imputation Model with Linear Regression and Predictive Mean Matching for sUA Imputation

The following example code will be used to perform multiple imputation to impute missing sUA for subjects with missing data due to site closure (due to COVID-19) for primary analysis:



[redacted]

Imputation Model with Logistic Regression for Response Imputation

The following example code will be used to perform multiple imputation to impute missing response outcomes for "Site Closure" subjects:

[redacted]

The following example code will be used to calculate the proportion of responders and standard error of the proportion for each treatment (for either imputation model listed above):

[redacted]

[redacted]

19.2. Cochran-Mantel-Haenszel Test

The following example code will be used to generate CMH analysis using datasets generated from PROC MI:

[redacted]

19.3. MI ANALYZE

The following example code will combine the 100 sets of statistics from the stratified analysis to get the estimate for proportion of responders and 95% CI for the proportion:

19.4. Mixed Model Repeated Measures (MMRM) Analysis of Covariance (ANCOVA) Model

The following example code will be used to generate the MMRM ANCOVA analysis:

[redacted]

19.5. Proportional Odds Logistic Model

The following example code will be used to generate the proportional odds logistic model for ordered categorical data:

[redacted]