Statistical Analysis Plan

Horizon Therapeutics Ireland DAC

HZNP-KRY-408

A Phase 4, Open-Label, Multicenter, Efficacy, Safety, Pharmacokinetics and Pharmacodynamics Trial of Intravenous KRYSTEXXA® (pegloticase) Administered Every 4 Weeks with Co-Administration of Weekly Doses of Methotrexate in Patients with Uncontrolled Refractory Gout (FORWARD Open-Label [OL] Trial)

Short Title: FORWARD OL

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Revision History

Version	Date	Document Owner	Revision Summary
1.0	25 MAY 2021		
2.0	08 DEC 2022	[redacted]	• Based on the protocol amendment, the possible second dose level of 24mg or 32 mg, changed to between 24 and 32 mg. [redacted] • Sample size updated from 30 to 40 subjects approximately 10-20 subjects per dose cohort) and 95% CI was updated accordingly. • In section for interim analysis and data monitoring, updated dose escalation rules • MTX exposure and person-year calculation at run in period are updated to use pegloticase on Day 1 as cut off for subjects received pegloticase, rather than use the last MTX dose in the run-in period. • Deleted handling the COVID-19 impact on the visit scheduled or discontinuation in efficacy analysis. • Added definitions for ADA positive and negative. • Removed summary of AEs of special interest reviewed by the internal safety review team. • Added definition for time-adjusted area under the sUA concentration curve from Day 1 to Week 24 and From Day 1 to Week 48. Added data summary for missing sUA imputed by baseline value. • Added data summary for missing sUA imputed by baseline value from proportion of time subjects sustained with sUA < 6 mg/dL from Day 1 to Week 24 and Day 1 to Week 48. • For laboratory and vital sing data, the summary will be conducted within 30 days (inclusive) form the later one of the last dose of pegloticase or MTX.

Approval

Upon review of this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

Signature	Date
DocuSigned by: [redacted] Signing Reason: I am the author of this document Signing Time: 09-Dec-2022 | 10:32 CST Study Biostatistician,	09-Dec-2022 | 10:32 CST
DocuSigned by: [redacted] 75BB6081599940258C8AF53FC19310E8 approve this document Signing Time: 09-Dec-2022 | 08:59 CST [redacted] Director, Biostatistics Horizon Therapeutics USA, Inc.	09-Dec-2022 | 08:59 CST
DocuSigned by: [redacted] on: I approve this document Signing Time: 08-Dec-2022 | 14:41 CST [redacted] E96A7E88BA664A1697D4C0C3F5DDD8B9 Sr. Medical Director, Rare Disease Horizon Therapeutics USA, Inc.	08-Dec-2022 | 14:41 CST

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Full Notation
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
AUC_{inf}	Area under the concentration-time curve from zero to infinity
AUC_{last}	Area under the concentration-time curve from zero to time t of the last measured concentration above the limit of quantification
BLQ	Below limit of quantification
BMI	Body mass index
CI	Confidence interval
CL	Oral clearance
C_{max}	Maximum serum concentration
C_{last}	Last quantifiable concentration
COVID-19	Coronavirus Disease 2019
CS	Clinically significant
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTC	Common Toxicity Criteria
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
FAAN	Food Allergy and Anaphylaxis Network
[redacted]	
hs-CRP	High-sensitivity C-reative protein
ICH	International Council for Harmonisation of Technical Reqirements for Pharmaceuticals for Human Use
IR	Infusion reaction
ITT	Intent-to-treat
IV	Intravenously
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate

Abbreviation	Full Notation
NCS	Not clinically significant
NIAID	National Institute of Allergy and Infectious Disease
PD	Pharmacodynamic(s)
PG	Polyglutamate
PK	Pharmacokinetic(s)
PP	Per protocol
PT	Preferred term
Q4 Wks	Every 4 weeks
QC	Quality control
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SMQ	Standard MedDRA query
SOC	System organ class
sUA	Serum uric acid
$t_{1/2}$	Apparent elimination half-life
TLFs	Tables, listings, and figures
V_{ss}	Steady state volume of distribution
Wk(s)	Week(s)

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Horizon Therapeutics Ireland DAC protocol HZNP-KRY-408 [A Phase 4, Open-Label, Multicenter, Efficacy, Safety, Pharmacokinetics and Pharmacodynamics Trial of Intravenous KRYSTEXXA® (pegloticase) Administered Every 4 Weeks with Co-Administration of Weekly Doses of Methotrexate in Patients with Uncontrolled Refractory Gout]. The purpose of this plan is to provide specific guidelines for the statistical analyses. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the statistical analysis plan (SAP):

- Protocol Version 4 Amendment 3, 13 April 2022

3. STUDY OBJECTIVES

3.1 Primary Objective

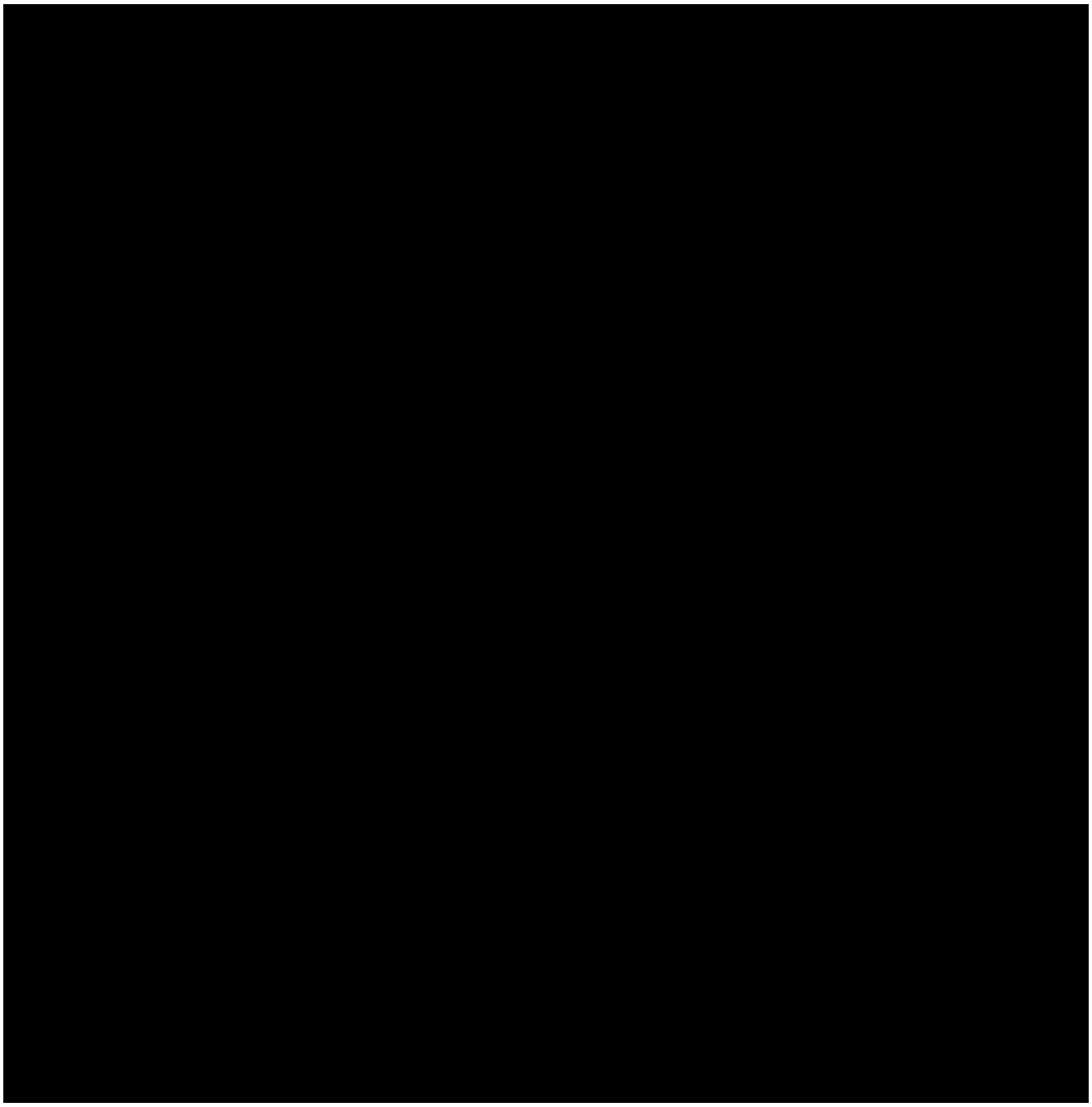
The primary objective is to choose a dose for further investigation by assessing the effect of up to 2 dose levels of pegloticase administered intravenously (IV) every 4 weeks (Q4 Wks), co-administered with weekly doses of oral methotrexate (MTX), as measured by the sustained normalization of serum uric acid (sUA) to < 6 mg/dL for at least 80% of the time during Month 6 and the duration of sUA to < 6 mg/dL over 24 week treatment period in adult subjects with chronic gout refractory to conventional therapy.

3.2 Secondary Objective

To assess the following of up to 2 dose levels of pegloticase (16 mg IV based on prior studies and a possible second dose level (between 24 mg and 32 mg IV) Q4 Wks co-administered with weekly doses of oral MTX in adult subjects with chronic gout refractory to conventional therapy:

- Pharmacokinetics (PK)
- Pharmacodynamics (PD):
    - Proportion of subjects with pre-infusion sUA levels < 6 mg/dL
    - Area under the sUA concentration vs. time curve from Day 1 to Week 24 and from Day 1 to Week 48.
    - Proportion of time subjects sustained sUA < 6 mg/dL from Day 1 to Week 24 or Day 1 to Week 48
- Profile of anti-uricase antibodies and anti-poly (ethylene glycol) antibodies

3.3 Exploratory Objectives



3.4 Safety and Tolerability Objectives

To assess the following of up to 2 dose levels of pegloticase (16 mg IV based on prior studies and a possible second dose level (between 24 mg IV and 32 mg IV) Q4 Wks co-administered with weekly doses of oral MTX in adult subjects with chronic gout refractory to conventional therapy:

- Adverse Event (AE)/Serious Adverse Event (SAE) profile overall for the combination of 4-weekly dosing of pegloticase and weekly MTX
    - Incidence of Adverse Events of Special Interest (AESI): Infusion-related reactions, anaphylaxis, gout flares, major adverse cardiovascular events (MACE) including type I and type II non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure
- Laboratory tests: hematology including complete differential, blood chemistry, and urinalysis
- Vital signs and physical examination

4. STUDY DESIGN AND PLAN

This is a Phase 4, open-label, multicenter, efficacy, safety, PK and PD trial of up to 2 dose levels of IV pegloticase infusions Q4 Wks, up to 6 IV infusions over 24 weeks (20 Wks + a 4 Wk end of trial visit), co-administered with weekly oral doses of MTX, to subjects with symptomatic chronic refractory gout. Subjects who may benefit from additional pegloticase treatment, may receive optional Q4 Wk dosing for an additional 6 infusions (Wk 24 through Wk 44 + a 4 Wk end of trial visit) for a total of 48 weeks. All subjects will be followed for approximately 4 weeks after their last infusion or after minimum of 3 months after their last dose of MTX (for non-vasectomized male participants).

The trial design will include 5 to 6 distinct components: 1) a Screening Period (screening should be completed within 35 days prior to Week -4); 2) a 4-week Run-In MTX Tolerability Assessment Period; 3) a 20-week Q4 Wks pegloticase + MTX Treatment Period which includes a Week 24/End of Trial/Early Termination (ET) Visit; 4) an optional extension Q4 Wks pegloticase + MTX Treatment Period from Week 24 to Week 44 if a subject might benefit from additional pegloticase treatment and at the discretion of the Investigator which includes a Week 48/End of Trial/Early Termination Visit; 5) an End of Pegloticase Infusions Visit (if applicable) within 2 weeks following the final infusion if the infusion is prior to Week 48; and 6) an End of Trial/Week 48/ET Visit. AE/SAE follow-up will occur at the subject's scheduled visit approximately 4 weeks after the last pegloticase infusion.

Those subjects that dose MTX and do not infuse pegloticase (screen failure/s) or early terminate from the trial for whom 4 weeks of safety follow-up is not available will be contacted (phone/email), if subject agrees, to assess AE/SAEs approximately 4 weeks post MTX dose or 4 weeks post ET date. Assessments will include if any AE/SAEs have occurred within the last 4 weeks and will confirm if any previous AE/SAEs have resolved.

All subjects who meet eligibility criteria at Screening will begin 15 mg MTX orally weekly at the Week -4 visit. Subjects must be able to tolerate the weekly dose of MTX 15 mg for 4 weeks to be eligible for the Day 1 pegloticase infusion. Subjects who are unable to tolerate the 15 mg dose of MTX during the 4 weeks preceding Day 1 will be considered MTX run-in screen failures.

For the first cohort, during the Pegloticase + MTX Period, pegloticase 16 mg will be administered IV Q4 Wks from Day 1 through the Week 20 Visit with an End of Trial Visit at Week 24 for a total of 6 infusions. An optional extension, at the discretion of both subject and investigator, will be available for continued infusions through the Week 44 Visit with an End of Trial Visit at Week 48 for a total of up to 12 infusions. Pegloticase will be administered after all pre-dose trial visit assessments have been completed at Day 1 and each Q4 Wk visit. The date of, and start and stop time of, each infusion will be recorded.

Serum uric acid stopping criteria will be applied: subjects with sUA level ≥ 6 mg/dL at 2 consecutive weekly visits beginning with the Week 1 visit, with observations 1 and 2 weeks after each infusion prioritized over sUA values 3 and 4 weeks after each infusion, must discontinue treatment (complete the End of Pegloticase Infusion visit procedures within 2 weeks, and continue subject visits according to the protocol (without pegloticase treatment)). sUA levels will be collected prior to and post infusion on the day of all infusions as well as weekly at each noninfusion visit until Week 24 then bi-weekly during the optional duration of the trial (Week 24 through Week 48). Given that the sUA may rise towards the end of the Q4 interval simply due to the pharmacokinetics of pegloticase, even without the impact of anti-drug antibodies (ADA), the 1- and 2-week post infusion values will be prioritized for the purpose of the stopping criteria.

Samples for measurement of sUA levels, PK analysis of pegloticase, pegloticase immunogenicity, and [redacted] analysis will be collected. 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.

Once the observations for the first two 4-week periods (Week 4 and Week 8) have been obtained from approximately the first 10 subjects in the first cohort, the data may be analyzed to determine if 1) 5 more subjects in the first cohort should be enrolled, 2) > 5 subjects should be enrolled in the first cohort, 3) enrollment in the first cohort should discontinue, and/or 4) enrollment for a second cohort should begin. This determination will be made based on assessment of the available 4- and 8-week pharmacokinetic, pharmacodynamic, efficacy, safety, and tolerability data from the first 10 subjects in the first cohort in concert with Horizon's internal standing FORWARD Trial Data Review Team.

If indicated, the second cohort of subjects will be recruited once all of the subjects in the first cohort have at a minimum their Week 4 and Week 8 assessments completed. Determination of the need for and the dose for a second cohort will be made based on a preliminary analysis of the efficacy and safety data from the first cohort.

For the second cohort, during the Pegloticase + MTX Period, pegloticase will be administered intravenously (IV) every 4 weeks from Day 1 through the Week 20 Visit for a maximum of 6 infusions over the Week 24 treatment period (Day 1 and Weeks 4, 8, 12, 16, and 20), with an optional extension through the Week 48 visit for a total of up to 12 infusions (at Weeks 24, 28, 32, 36, 40, and 44). All trial procedures for this cohort will be performed similarly to those for the first cohort.

5. DETERMINATION OF SAMPLE SIZE

A sample size of up to approximately 40 subjects (approximately 10-20 subjects per dose cohort) is planned for this trial. With 10 subjects assessed at a given dose level, an observed response rate for a dichotomous endpoint of 70% (7/10) will provide a two-sided 95% confidence interval with a lower bound of approximately 35%. If 20 subjects are assessed at a given dose level, an observed response rate of 70% (14/20) will provide a two-sided 95% confidence interval with a lower bound of approximately 46%.

In general, subjects that prematurely discontinue from the trial for any reason will not be replaced. An exception may be made for subjects who are unevaluable due to the impact of the COVID-19 pandemic and associated restrictions on movement and work. Subjects unable to receive treatment or be evaluated due to restrictions during the COVID-19 pandemic may be replaced, at the discretion of the sponsor. This may result in more subjects than originally planned to be enrolled into the trial to allow for the originally planned number to be evaluable for the primary efficacy analysis.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation (ICH) numbering convention will be used for all TLFs. Unless otherwise noted, all statistical testing will be 2-sided and will be performed at the 0.05 significance level.

Continuous variables will be summarized by presenting the number of observations, means, standard deviations (SDs), medians, quartiles, minimums, and maximums.

Categorical variables will be summarized by presenting counts and percentages of subjects in corresponding categories. All possible categories as defined in the CRF should be populated, even if they have zero counts. Percentages are based on the total number of subjects unless otherwise specified.

All summary tables will be presented by cohort. Baseline summaries will also include a total summary column where relevant. If subjects are enrolled into a cohort at a shorter infusion duration (60 minutes) then tables will be presented by cohort and infusion duration.

Individual subject data obtained from the eCRFs, external vendors, and any derived data will be presented by subject in data listings.

The analyses described in this plan are considered a priori, in that they have been defined before database lock.

Any analyses performed after database lock will be considered post hoc and exploratory. Post hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS® software Version 9.4 or higher. Tables, listings, and figures will be presented in RTF format.

7. 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 eCRF. The reference date associated with each visit is collected on the Visit Date eCRF page. Further, the End of Study/Early Termination (ET) visit and the End of Pegloticase Infusion Visit will be windowed to a visit based on the study day of occurrence relative to the target day of each scheduled visit according to Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7 below. In the event that an End of Study/ET or End of Pegloticase Infusion 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 Infusion visit will not be summarized. Table 1 shows windows for the vital sign assessments. Table 2 shows windows for the hematology and chemistry clinical laboratory assessments. [redacted] Table 5 show windows for the ADA assessments. Table 6 shows windows for pegloticase PK assessments. Table 7 shows windows for sUA assessments. For all assessments, the study day in the Pegloticase + MTX period will be calculated relative to the first dose of pegloticase.

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

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 4	29	2 – 43
	Week 8	57	44 – 71
	Week 12	85	72 – 99
	Week 16	113	100 – 127
	Week 20	141	128 – 155
	Week 24	169	156 – 183
	Week 28	197	184 – 211
	Week 32	225	212 – 239
	Week 36	253	240 – 267
	Week 40	281	268 – 295
	Week 44	309	296 – 323
	Week 48	337	≥324

Table 2: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (Hematology and Chemistry Laboratory Assessments)

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 2	15	2 – 22
	Week 4	29	23 – 43
	Week 8	57	44 – 71
	Week 12	85	72 – 99
	Week 16	113	100 – 127
	Week 20	141	128 – 155
	Week 24	169	156 – 211
	Week 36	253	212 – 295
	Week 48	337	≥296

Table 5: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (Antibody Assessments)

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 2	15	2 – 22
	Week 4	29	23 – 43
	Week 8	57	44 – 85
	Week 16	113	86 – 41
	Week 24	169	142 – 211
	Week 36	253	212 – 295
	Week 48	337	≥296

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

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 1	8	2 – 11
	Week 2	15	12 – 18
	Week 3	22	19 – 25
	Week 4	29	26 – 36
	Week 6	43	37 – 46
	Week 7	50	47 – 53
	Week 8	57	54 – 85
	Week 16	113	86 – 141
	Week 22	155	142 – 162
	Week 24	169	163 – 211
	Week 36	253	212 – 295
	Week 48	337	≥296

Table 7: Visit Windows for Assigning ET and End of Pegloticase Visits to a Scheduled Visit (sUA Assessments)

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 1	8	2 – 11
	Week 2	15	12 – 18
	Week 3	22	19 – 25
	Week 4	29	26 – 32
	Week 5	36	33 – 39
	Week 6	43	40 – 46
	Week 7	50	47 – 53
	Week 8	57	54 – 60
	Week 9	64	61 – 67
	Week 10	71	68 – 74
	Week 11	78	75 – 81
	Week 12	85	82 – 88
	Week 13	92	89 – 95
	Week 14	99	96 – 102
	Week 15	106	103 – 109
	Week 16	113	110 – 116
	Week 17	120	117 – 123
	Week 18	127	124 – 130
	Week 19	134	131 – 137
	Week 20	141	138 – 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
	Week 36	253	247 – 260
	Week 38	267	261 – 274
	Week 40	281	275 – 288
	Week 42	295	289 – 302
	Week 44	309	303 – 312
	Week 45	316	313 – 319
	Week 46	323	320 – 330
	Week 48	337	≥338

8. ANALYSIS SETS

The following subject analysis sets will be used for safety analyses:

- The safety analysis set will include all enrolled subjects who take at least 1 dose of pegloticase + MTX.
- The MTX analysis set will include all subjects who take at least 1 dose of MTX.

The following subject analysis sets will be used for efficacy analyses:

- The intent-to-treat (ITT) analysis set will include all enrolled subjects who have at least 1 scheduled assessment on Day 1.
- The per-protocol (PP) analysis set will include all enrolled subjects who receive at least 1 dose of pegloticase, are taking the 15 mg dose of MTX at the time of first pegloticase dose and have no major protocol deviations that would challenge the validity of the data.

If the ITT analysis set and the PP analysis set are the same, then analysis results and summaries based on only the ITT analysis set will be provided.

The following analysis set will be used for PK analyses:

- PK analysis set will include all enrolled subjects who receive at least one dose of pegloticase and have a post-pegloticase sample evaluable for PK analysis.

9. STUDY POPULATION

9.1 Subject Disposition

The number of subjects screened, the number of screen failures, the number of subjects who entered the MTX Run-in period and the number of subjects who discontinued the MTX Run-in period will be summarized. The number of subjects in each analysis set, the number of subjects who entered the Pegloticase + MTX treatment period, the number of subjects who completed and discontinued from the Pegloticase + MTX treatment period (separately for Weeks 1-24 and the optional period Weeks 24-48), and the number of subjects who completed and discontinued the study, along with the reasons for discontinuation for Week 24 and Week 48 respectively will be summarized.

Subject study duration in weeks will be summarized for subjects in the ITT analysis set. The number of subjects with results for each scheduled visit will also be presented. A subject will be considered to have completed a visit if they had any results recorded in the eCRF for the visit. Subject study duration will be calculated from the first visit in the MTX Run-in Period (Week -4) to the end of trial visit date, on which the end of study assessment (i.e., Week 48) is performed.

9.2 Protocol Deviations

Major protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified before database lock. Major protocol deviations are detailed in the Protocol Deviation Management Plan and may include, but are not limited to:

- Subjects who did not satisfy selected key inclusion and exclusion criteria;
- Subjects who developed withdrawal criteria during the study but were not withdrawn;
- Subjects who received the wrong treatment or an incorrect dose;
- Subjects who received an excluded concomitant treatment.

The decision whether a subject is excluded from the PP analysis set due to a protocol deviation will be made prior to database lock.

The number of subjects experiencing any minor and any major protocol deviation, along with the number of protocol deviations, will be presented for subjects in the ITT analysis set by cohort and overall. Major protocol deviations will be further summarized by deviation category.

All protocol deviations, including the deviation designation (major or minor), category, subcategory, indication of whether the deviation led to an exclusion of a subject from the PP analysis set and indication of whether the deviation was related to COVID-19 will be presented in a data listing. A separate listing of deviations related to COVID-19 will also be presented.

9.3 Eligibility

A listing of subjects not fulfilling all eligibility criteria will be created.

9.4 Demographic and Baseline Characteristics

Demographic and baseline data and gout history will be summarized using descriptive statistics by cohort.

Demographic variables include age (in years), sex, ethnicity and race.

Other baseline characteristics include height (in cm), weight (in kg), body mass index (BMI in kg/m^2), childbearing potential (for females only), reason not of childbearing potential (if applicable), and substance use history (including alcohol).

Descriptive statistics will be presented for age, height, weight and BMI. Frequency counts and percentages will be presented for sex, ethnicity, race, childbearing potential (for females only), reason not of childbearing potential, tobacco use, alcohol use, and other substance use. Demographic and baseline characteristics will be summarized by cohort and overall for the ITT and safety analysis sets.

Gout history variables will include time since first gout attack (in years), time since first gout diagnosis (in years), presence of uric acid crystals confirming diagnosis, number of acute flares

in past 12 month, number of acute flares in past 6 months, number of acute flares in past month, pattern of flares, typical severity of acute flares, chronic gout synovitis/arthropathy, prior or current tophi, history of overnight hospital stay for gout, history of surgery for gout (excluding arthrocentesis), history of kidney stones, number of episodes of renal colic in the past year, kidney function impacted by gout, and urate lowering therapy history (allopurinol, febuxostat, and other urate lowering therapy for gout).

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

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

Gout history will be summarized by cohort and overall for the ITT and safety analysis sets.

Medical history

The verbatim term of the medical/surgical history condition/event will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 23.1.

A summary table will be prepared by cohort and in total based on the ITT analysis set. The summary will be ordered alphabetically by system organ class (SOC) and by preferred term (PT) within system organ class.

Medical history terms and tobacco and alcohol history will be listed.

9.5 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to Anatomical Therapeutic Chemical (ATC) level 4 and preferred names using the WHODRUG Global B3 Sep2020.

Partial dates will be imputed. For details on imputation rules, refer to Appendix A: Presentation of Data and Programming Specifications. Imputed dates are only used for classification of medication into prior or concomitant medication; no other calculation such as durations will be done.

Prior medications are defined as any medication with a start date prior to the date of first dose of treatment in the MTX Run-in Period.

Concomitant medications during the MTX Run-in Period are defined as:

- Medications with a start prior to the first dose of MTX in the MTX Run-in Period that are ongoing or with a stop date after the first dose of MTX in the MTX Run-in Period.
- Medications with a start date after the first dose of MTX in the MTX Run-in Period but before the first dose of pegloticase and before 30 days after the last MTX dose, for subjects who did not receive an infusion of pegloticase.

Concomitant medications during the Pegloticase + MTX Period are defined as:

- Medications with a start prior to the first dose of pegloticase that are ongoing or with a stop date after the first dose of pegloticase.
- Medications with a start date after the first dose of pegloticase but before 30 days after the last dose of pegloticase.

Medications with a partial start date where month and year of start match the month and year of first MTX date and match the month and year of first Pegloticase infusion will be classified as being concomitant in both the MTX Run-in Period and in the Pegloticase + MTX Period. In general, medications can be classified in one or more of prior, concomitant during the MTX Run-in Period, and concomitant during the Pegloticase + MTX Period categories.

Summaries will be presented separately for prior medications, concomitant medications during the MTX Run-in Period, and concomitant medications during the Pegloticase + MTX Period. Summaries will be presented by 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.

10. EFFICACY ANALYSES

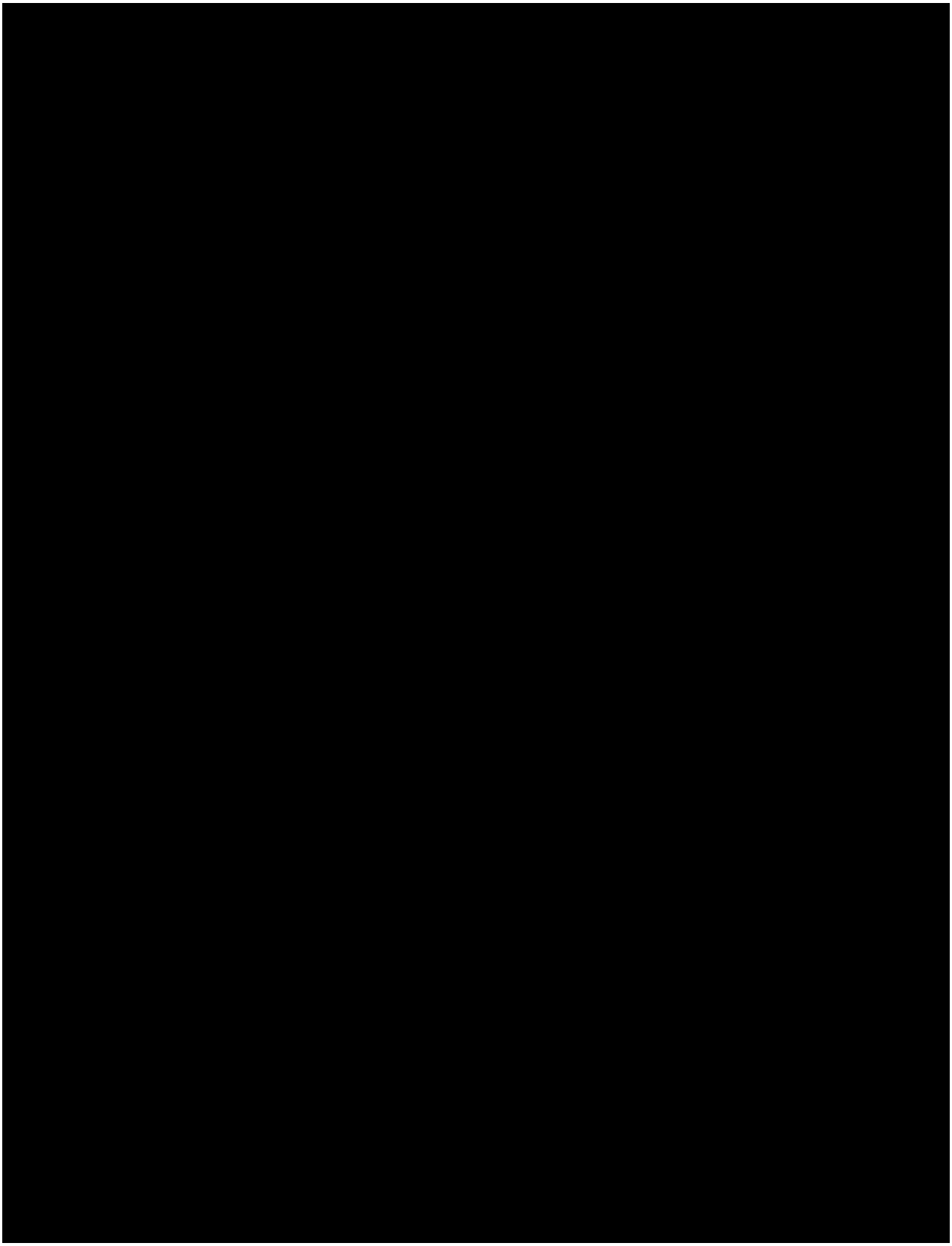
The ITT analysis set will be used to assess efficacy endpoints. Selected efficacy endpoints may also be assessed in the PP analysis set. If the ITT analysis set and the PP analysis set are the same, then analysis results and summaries based on only the ITT analysis set will be provided.

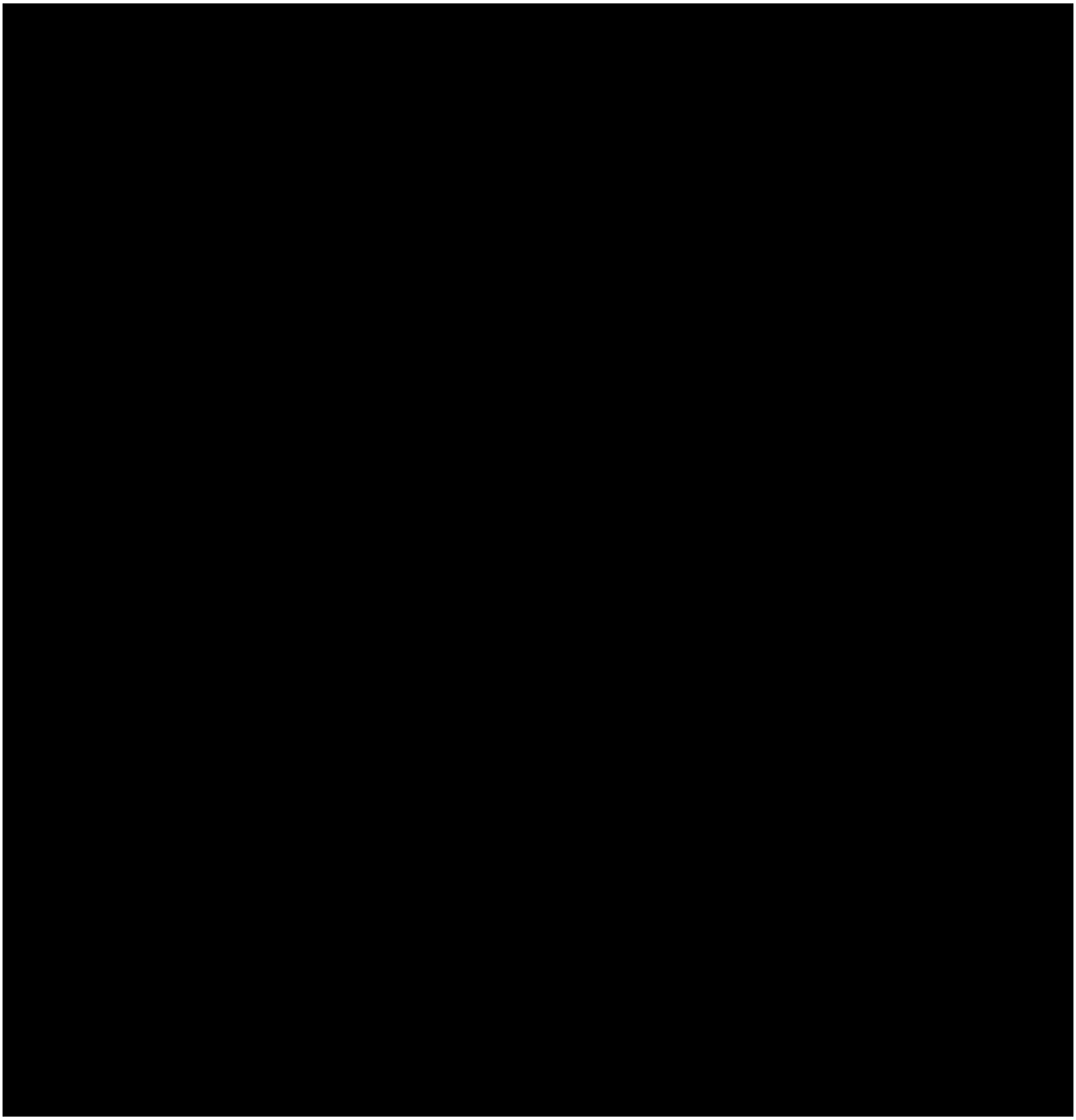
The estimand for the primary analysis will use the Treatment Policy Strategy. That is data will be used regardless of whether an intercurrent event (such as discontinuation of treatment) occurred.

10.1 Efficacy Variables

Efficacy variables include:

- Month 6 responder rate – defined as the proportion of subjects achieving and maintaining sUA < 6 mg/dL for at least 80% of the time during Month 6. The Month 6 responder rate will consider pre and post infusion results at Week 20, results at Week 21, Week 22, and Week 23, and pre-infusion results at Week 24. The amount of time that sUA is < 6 mg/dL (using linear interpolation if necessary) will be calculated and divided by the total amount of time from the first to the last observed sUA value in corresponding time range (missed values in this time range will be ignored for purposes of this calculation). If the amount of time that sUA is < 6 mg/dL is ≥ 80%, then the subject will be considered a responder.
- Time to first sUA ≥ 6 mg/dL after first achieving sUA < 6 mg/dL – defined as the time from the first sUA result < 6mg/dL to the first subsequent result that is ≥ 6 mg/dL. Subjects who do not have a subsequent result ≥ 6 mg/dL will be censored on the date of





10.2 Baseline Values

Unless otherwise noted, baseline is defined as the last non missing value recorded before the first infusion of pegloticase.

10.3 Adjustments for Covariates

Analyses of the efficacy endpoints will not include adjustments for covariates.

10.4 Handling of Dropouts or Missing Data

No imputations will be made for missing values, unless specified otherwise. In general, summaries will be based on observed data only. See further details on missing data for the primary endpoint in Section 11.2.

10.5 Interim Analysis and Data Monitoring

No formal interim analysis is planned for this study.

Once the observations for the first two 4-week periods (i.e., Week 4 and Week 8) have been obtained from approximately the first 10 subjects in the first cohort, the data may be analyzed to determine one of the followings:

1) Keep the the same dose with:
   a) additional subjects enrolled at the same dose, or
   b) the change in the infusion duration from 120 minutes to 60 minutes,

2) Escalate the dose to between 24 mg and 32 mg Q4 Wks as the second cohort. The infusion duration may change from 120 minutes to 60 minutes.

3) Pause and re-evaluate the trial for safety concerns.

This determination will be made based on assessment of the available 4- and 8-week pharmacokinetic, pharmacodynamic, efficacy, safety and tolerability data from the first 10 subjects in the first cohort. If additional subjects are enrolled in Cohort 1, determination of the need and the dose level for the second cohort will be made based on an additional analysis of available 4- and 8-week PK, PD, efficacy and safety data for all subjects in Cohort 1.

10.6 Examination of Subgroups

No subgroup analysis is planned for this study.

10.7 Multiple Comparison/Multiplicity

Data will be summarized on a regular basis for purposes of planning future cohorts, with no Type I error rate adjustments made due to multiple summaries.

No adjustments will be made for the multiple doses assessed.

No adjustments will be made for the adaptive sample size (decision to enroll an additional 5 subjects, based on data from the first 10 subjects treated at a given dose).

10.8 Multicenter Studies

Data from all sites will be summarized together for analyses.

11. METHODS OF EFFICACY ANALYSIS

11.1 Handling Rules for sUA Values

Serum samples for measurement of sUA levels will be collected prior to and post infusion on the day of all infusions as well as weekly at each non-infusion visit until Week 24; then bi-weekly during the optional duration of the trial (Week 24 through Week 48). Subjects with a pre-infusion sUA level > 6 mg/dL at 2 consecutive study visits beginning with the Week 1 Visit may discontinue pegloticase and complete the End of Pegloticase Infusions Visit (if applicable) or the Week 24/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 or lower and equal than the lab assay's limit of quantification (e.g. "< 0.02" or . "<= 0.02"), zero will be used as the numeric value for the purpose of determining response and for summaries of observed values and the change from baseline. When the central laboratory or local laboratory reports a value for sUA as being higher, higher and equal, lower and equal than a certain value of quantification (e.g. "> 8.7" or ">= 8.7"), the numeric value (e.g. 8.7) after ">" or ">=" is used for the purpose of determining response and for summaries of observed values and the change from baseline.

11.2 Primary Efficacy Endpoint and Analysis

The first co-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 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, non-infusion, and post-infusion samples with non-missing sUA values. Central laboratory results from visits at which an infusion was not performed (e.g., subject discontinued pegloticase but remained in study or unscheduled visits) will be used when available.

An estimate of proportion of time the sUA < 6 mg/dL will be determined by connecting a subject's neighboring data points with a straight line. If the sUA curve goes from below 6 mg/dL to above 6 mg/dL, linear interpolation will be used to estimate the time at which the sUA curve intersects 6 mg/dL, using the last sample collected that was < 6 mg/dL and the first sample that was > 6 mg/dL. Analogously, if the sUA curve goes from above 6 mg/dL to below 6 mg/dL, linear interpolation will be used to estimate the time at which the sUA curve intersects 6 mg/dL, using the last sample that was above 6 mg/dL and the first value < 6 mg/dL after the SUA had been above 6 mg/dL.

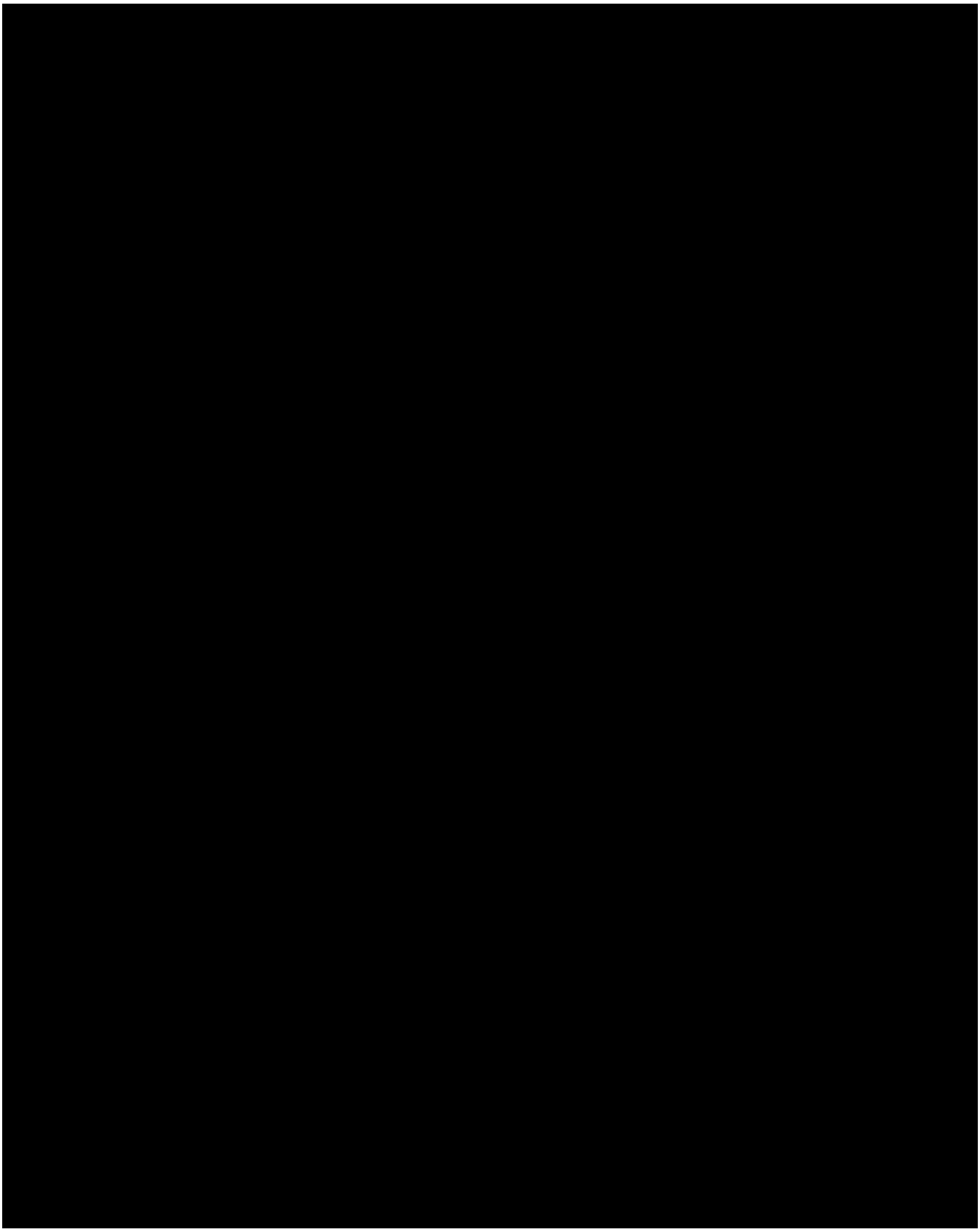
There will be no imputation of sUA values due to missed collections between Week 20 and Week 24. Only observed values will be included in the calculation. If central lab results are available, central lab results are used. If central lab results are not available, local lab results will be used. If only one sUA result is collected during the Month 6 period, response will be based on the single value being strictly < 6 mg/dL.

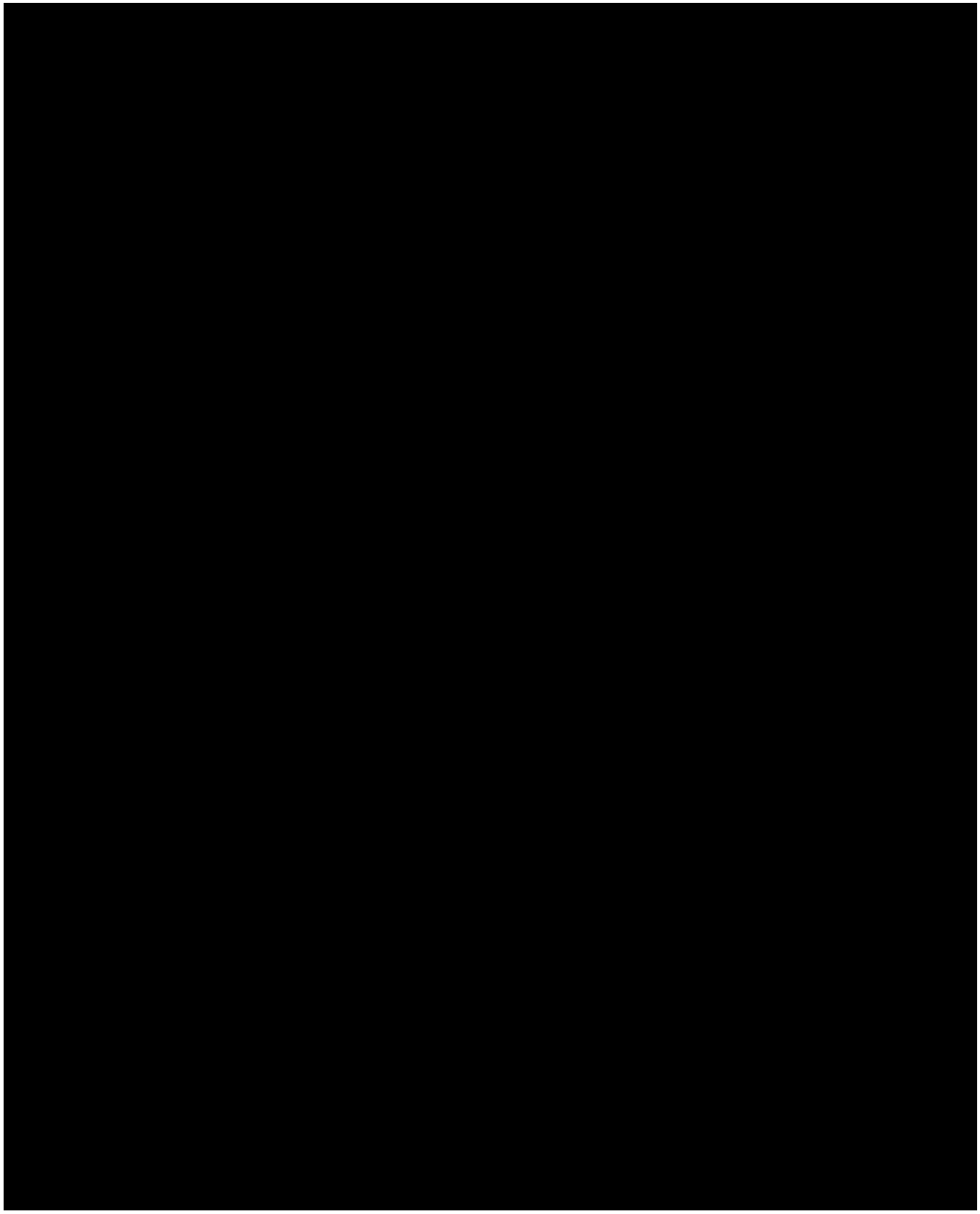
Let T1 = the number of elapsed hours between the first and last non-missing sUA concentration among those collected between Week 20 and Week 24 collections.
Let W1 = the number of hours among the T1 hours where the sUA concentration was below 6 mg/dL.
The proportion of hours $P = 100 * \frac{W1}{T1}$
If the subject's proportion of hours, P, is greater than or equal to 80% the subject will be called a responder for the primary efficacy endpoint. A subject with the proportion of hours, P, less than 80% will be counted as a non-responder. Any subject who meets the sUA stopping rules (i.e., the subject has two consecutive pre-infusion sUA values > 6 mg/dL starting at Week 1) prior to Week 24 will be counted as a non-responder.

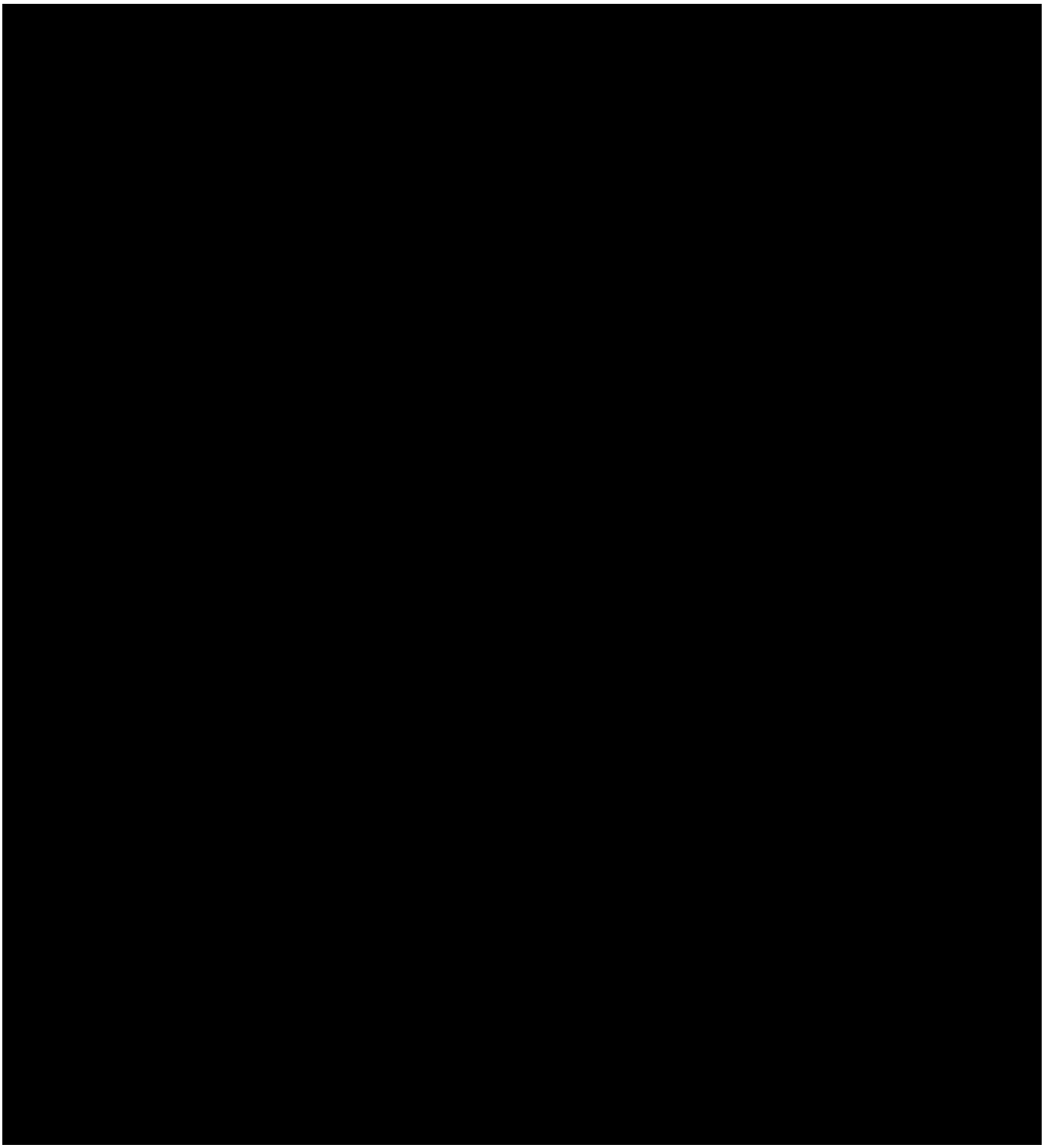
The proportion of hours during the period during which the sUA was less than 6 mg/dL will be summarized using descriptive statistics. If a subject has ≤ 1 data point in the period, then the proportion of hours will not be calculated. The number and proportion of subjects that discontinued treatment due to the stopping rule will be summarized. The number and proportion of responders will be summarized along with a 95% exact (Clopper-Pearson) confidence interval (CI) for the proportion. In addition, the number and proportion of subjects missing all data in analysis period, subjects with only one measurement (above cutoff) in analysis period, and subjects with only one measurement (below cutoff) in analysis period will be summarized.

The Month 6 responder analysis will be performed using the ITT and PP analysis sets.

The second co-primary efficacy endpoint is the time to first sUA ≥ 6mg/dL (in days) after achieving sUA < 6 mg/dL from the first pegloticase infusion until Week 24. This will be summarized using Kaplan-Meier estimates of the median time to event and corresponding 95% CIs for the ITT and PP analysis sets. Subjects who do not have a subsequent result ≥ 6 mg/dL will be censored on the date of their last observed sUA result. Subjects who do not achieve a sUA result < 6 mg/dL will be excluded from the analysis. The time to event for subjects who experience the given event will also be summarized using descriptive statistics.







12. PHARMACOKINETIC ANALYSES

All PK analyses will be summarized in the PK Analysis Set.

12.1 Data Handling

For all subjects, serum samples for PK analysis will be collected after the end of infusion on Day 1, at Week 1, Week 2, Week 3, prior to the pegloticase infusion and after the end of infusion at Week 4, at Week 6 and Week 7, prior to the pegloticase infusion and post the infusion at Weeks 8 and 16, at Week 22, prior to and post the pegloticase infusion at Week 24, and prior to and post the pegloticase infusion at Week 36. Additional PK samples will be collected at the End of Pegloticase infusion Visit and Week 48/End of Trial/Early Termination visit.

The observed serum concentration data will be handled as follows:

- For post-dose samples, the planned sampling time will be used in summary tables.
- Concentrations below the limit of quantification (BLQ) collected on Day 1 pre-dose will be summarized as zero. All other concentrations BLQ will be excluded from the analysis summaries.
- Missing post-dose values will not be imputed.

12.2 Presentation of Pegloticase Serum Concentrations

Individual serum concentration results:

A data listing will be provided displaying the concentration as reported and the nominal and actual sampling times relative to start of dose administration. Results will be displayed using 3 significant digits.

Summary statistics of serum concentrations:

The serum concentrations for pegloticase will be summarized by the nominal time points, baseline ADA status (positive vs negative, if each group has at least three subjects) and by cohort (if the second cohort is enrolled) using descriptive statistics (n, arithmetic mean, SD, median, minimum, maximum, Q1, Q3, geometric mean, and coefficient of variation (CV) % for the geometric mean).

Results will be displayed using 3 significant digits.

The CV % for the geometric mean will be calculated using the following formula:

$$CV\ (\%) = 100 * \sqrt{e^{SD_{ln}{}^2} - 1}$$

where SD_{ln} = standard deviation of the natural-log transformed data.

Mean (SD) concentration-time (nominal time) plots will be generated for PK data after the 1st dose of pegloticase (including results at Day 1, Week 1, Week 2, Week 3, and Week 4 pre-infusion PK data).

12.3 Determination and Analysis of Pegloticase PK Parameters

Noncompartmental PK parameters of pegloticase will be estimated using concentration data after the first dose (including Week 4 predose concentration data) using Phoenix WinNonlin® software. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, serum concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0. Samples that are BLQ prior to the achievement of the first quantifiable concentration after the first pegloticase dose will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin.

Pharmacokinetic parameters such as AUC_{inf}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

The following PK parameters will be derived, as appropriate based on available data:

- **C_{max}** (µg/mL) – maximum observed concentration
- **C_{last}** (µg/mL) – last quantifiable concentration determined directly from individual concentration-time data
- **$t_{1/2}$** (hr) – terminal elimination half-life, calculated as ln (2)/λ_z
- **AUC_{last}** (µg•hr/mL) – area under the concentration-time curve from time zero to the time of the last quantifiable concentration
- **AUC_{inf}** (µg•hr/mL) – area under the concentration-time curve from time zero extrapolated to infinite time
- **V_{ss} (mL) –** steady state volume of distribution
- **CL** (mL/h) –clearance

Individual PK parameters:
A raw data listing will be provided displaying the individual PK parameters. Results will be displayed using 3 significant digits. Intervals (hours) used for determination of serum pegloticase λz will also be listed.

Summary statistics of PK parameters:
Pharmacokinetic parameters will be summarized by cohort using descriptive statistics (n, arithmetic mean, SD, CV % for the arithmetic mean, median, Q1, Q3, minimum, maximum, geometric mean, and CV % for the geometric mean). Pegloticase PK parameters (AUC, Cmax, CL and $t_{1/2}$) will also be summarized by baseline ADA status (positive vs negative) if there are at least three subjects in each group. ADA positive is defined as positive for anti-PEG or anti-uricase antibodies at any visit during the study and ADA negative is defined as negative for both anti-PEG and anti-uricase antibodies for all visits during the study.

Results will be displayed using 3 significant digits.

[redacted]

13. IMMUNOGENICITY ANALYSES

Pegloticase immunogenicity will be assessed by incidence and titers of anti-PEG and anti-uricase IgG antibodies prior to the pegloticase infusion on Day 1, Week 2, Week 4, Week 8, Week 16, Week 24, Week 36, Week 44, end of pegloticase infusion visit if prior to Week 44, and Week 48.

The following summaries will be presented for anti-PEG IgG antibodies:

- Number and percentage of subjects with ADA positive at baseline
- Number and percentage of subjects with ADA positive at post-baseline and negative at baseline or subjects with ADA positive at baseline and post-baseline with an increase in titer from baseline, for each post-baseline visit and for any post-baseline visit
- Number and percentage of subjects with ADA positive at post-baseline and negative at baseline, for each post-baseline visit and for any post-baseline visit
- Number and percentage of subjects with ADA positive at baseline and post-baseline with an increase in titer from baseline, for each post-baseline visit and for any post-baseline visit

For anti-uricase IgG antibodies, the number and percentage of subjects with ADA positive at each post-baseline visit and overall for any post-baseline visit will be presented.

The mean and CV of titers will be presented by visit for both anti-PEG and anti-uricase IgG antibodies.

14. SAFETY ANALYSES

Safety analyses for the MTX Run-in Period will be based on the MTX Analysis Set. Safety analyses for the Pegloticase + MTX Period will be based on the Safety Analysis Set.

14.1 Extent of Exposure

Study drug exposure will be summarized for both MTX and pegloticase using the duration of treatment (in days), number of doses, and total dosage received.

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

- Duration of treatment is defined as the last dose date of MTX – first dose date of MTX + 1 for subjects who do not continue into the Pegloticase + MTX Treatment Period and defined as the first dose date of pegloticase – the first dose date of MTX for subjects who continue into the Pegloticase + MTX period
- Total MTX dosage taken between the first and last dose dates in the MTX Run-in Period, inclusive (in mg)
- Average MTX dose (in mg) (total dosage for the MTX Run-in Period divided by number of doses taken during the MTX Run-in Period)
- Number of subjects with MTX dosage reductions from planned 15 mg/week for reason of AE, abnormal labs, or titration down.

For the Pegloticase + MTX Period, the following will be summarized:

- Pegloticase
    - Number of pegloticase infusions received overall
    - Duration in days between first and last pegloticase infusion, defined as last infusion date – first infusion date + 1
    - Number of incomplete infusions received
    - Number of interrupted infusions
- At each scheduled Pegloticase infusion visit
    - Number of subjects receiving a complete infusion (i.e., full dose administered)
    - Number of infusions administered without interruption
    - Number of subjects with an interrupted infusion
- MTX
    - Duration of MTX dosing during the Pegloticase + MTX Period, defined as the last MTX dose date – first pegloticase dose date + 1
    - Cumulative MTX dosage (in mg) received during the Pegloticase + MTX period
    - Average MTX dose (in mg) (total dosage for the Pegloticase + MTX Period divided by number of doses taken during the Pegloticase + MTX Period)
    - Number of subjects with MTX dosage reductions from planned 15 mg/week.

For the overall study, the following will be summarized:

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

Methotrexate administration and pegloticase infusion details will be listed. The use of prophylaxis treatments will be provided in listings only.

14.2 Adverse Events

Treatment-emergent AEs (TEAEs) will be summarized separately for the MTX Run-in Period using the MTX Analysis Set and for the Pegloticase + MTX Period using the Safety Analysis Set. TEAEs during the MTX Run-In Period are defined as events with an onset date on or after the first dose of MTX through the first pegloticase infusion, or through 4 weeks after the last dose of MTX for subjects who do not receive pegloticase. TEAEs during the Pegloticase + MTX Period are defined as events that occur after the start of the first pegloticase infusion through 4 weeks after the last dose of pegloticase and MTX (whichever is later).

Partial dates will be imputed. For details on imputation rules, refer to Appendix A: Presentation of Data and Programming Specifications. Imputed dates are only used for classification of TEAEs. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such.

Events with missing relationship to study drug in the MTX Run-in period will be considered related to MTX. Events with missing relationship to study drug in the Pegloticase + MTX period will be considered “related” to MTX and “related” to pegloticase. Missing severities will be considered severe.

Verbatim terms in the eCRFs will be mapped to PTs and SOCs using the MedDRA version 23.1. Adverse event severity will be graded according to Rheumatology Common Toxicity Criteria (CTC) v2.0 [Woodworth et al, 2007].

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

- TEAEs
- Serious TEAEs
- TEAEs Related to MTX
- TEAEs Related to pegloticase (applicable to Pegloticase + MTX Period only)
- Serious TEAEs Related to MTX

- Serious TEAEs Related to pegloticase (applicable to Pegloticase + MTX Period only)
- TEAEs with a Rheumatology CTC grade of 3 or higher
- TEAEs leading to permanent withdrawal of MTX
- TEAEs leading to permanent withdrawal of pegloticase (applicable to Pegloticase + MTX Period only)
- TEAEs Related to MTX leading to permanent withdrawal of MTX
- TEAEs Related to pegloticase leading to permanent withdrawal of pegloticase (applicable to Pegloticase + MTX Period only)
- TEAEs leading to death

The following summaries will be presented:

- Subject incidence of TEAEs and total number of unique TEAEs along with the event incidence rate by MedDRA SOC and PT, for the MTX Run-in Period and Pegloticase + MTX Period
- Subject incidence of TEAEs by MedDRA SOC, PT, and maximum Rheumatology CTC grade, for the MTX Run-in Period and Pegloticase + MTX Period. At each level of subject summarization, a subject is classified according to the maximum grade if the subject reported 1 or more events.
- Subject incidence of TEAEs by MedDRA SOC, PT, and closest relationship to MTX (Related/Not Related), for the MTX Run-in Period and Pegloticase + MTX Period. At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported 1 or more events. Adverse events with a missing relationship will be considered related for this summary.
- Subject incidence of TEAEs by MedDRA SOC, PT, and closest relationship to pegloticase (Related/Not Related), for the Pegloticase + MTX Period. At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported 1 or more events. Adverse events with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA SOC and PT, for the MTX Run-in Period and Pegloticase + MTX Period
- Subject incidence of TEAEs leading to MTX discontinuation and total number of unique TEAEs leading to MTX discontinuation by MedDRA SOC and PT, for the MTX Run-in Period and Pegloticase + MTX Period
- Subject incidence of TEAEs leading to pegloticase discontinuation and total number of unique TEAEs leading to pegloticase discontinuation by MedDRA SOC and PT, for the Pegloticase + MTX Period
- Subject incidence of COVID-19 related TEAEs (identified using the COVID-19 SMQ, narrow terms only) and total number of unique COVID-19 related TEAEs along with the

event incidence rate by MedDRA SOC and PT, for the MTX Run-in Period and Pegloticase + MTX Period

Each AE summary will be displayed overall for the MTX Run-in Period and by cohort for the Pegloticase + MTX Period. Summaries that are displayed by SOC and preferred terms (PT) will be ordered alphabetically by SOC and by PT within SOC. Event incidence rates will be calculated as the (number of events divided by the total patient-years of exposure to the study drug)*100. The patient-years of exposure for the MTX Run-in Period for each subject will be derived as (first dose date of pegloticase (Day 1) – first dose date of MTX)/365.25 if subjects receive pegloticase, and (last dose date of MTX – first dose date of MTX +1)/365.25 if subject do not receive pegloticase. The patient-years of exposure for the Pegloticase + MTX Period for each subject will be derived as (last dose date of MTX or pegloticase (whichever is later) in the Pegloticase + MTX Period – first dose date of pegloticase + 1)/365.25.

The proportion of subjects experiencing each SAE and each AESI will be summarized for each cohort, along with the cohort difference in proportions and corresponding 95% CI for the cohort difference.

All AEs will be listed. SAEs, AEs leading to death, AEs leading to permanent withdrawal of MTX, and AEs leading to permanent withdrawal of pegloticase will also be listed.

14.3 Adverse Events of Special Interest

Adverse events of special interest will include: infusion reactions (IRs), anaphylaxis, gout flares, and MACE including type I and type II non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure.

IRs and Anaphylaxis

IRs and anaphylaxis reactions are identified by the investigator on the eCRF. The signs and symptoms associated with each event are entered on the eCRF and will be coded to the MedDRA dictionary. IRs and anaphylaxis events, and the associated signs and symptoms, will be summarized in the pegloticase + MTX Period by SOC, PT, severity, and the time relative to the most recent pegloticase infusion. Time relative to the most recent pegloticase infusion will be categorized as: during infusion, ≤ 2 hours after infusion, > 2 hours to 24 hours after infusion, > 24 hours after infusion, and missing (time of event is missing).

IRs and anaphylaxis events will also be reviewed by the Horizon internal safety review team.

The following search algorithm will be used to identify possible IR and anaphylaxis cases:

Infusion Reaction

- All IRs reported by investigators based on the protocol definition and reported on the eCRF.
- All other AEs that occur after start of infusion and up to 24 hours following the end of the infusion or on the same day of infusion if the start time is missing.

Anaphylaxis

- Any anaphylaxis reported by investigators based on the NIAID/FAAN criteria and reported on the eCRF.
- Any anaphylactic reactions identified by the algorithmic MedDRA SMQ Anaphylactic reactions.

The number and percentage of subjects with infusion related reactions including anaphylaxis by the investigator reported 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:
    - ADA positive during post-baseline treatment period is defined as
        - Negative at baseline and positive at any post-baseline timepoint, or
        - Positive at baseline and had an increase in titer from baseline
    - ADA negative during post-baseline treatment period is defined as
        - Negative at all time points
        - Positive at baseline, but titer did not increase from baseline

Cardiovascular Events

Cardiovascular events will include Major Adverse Cardiovascular Events (MACE), including non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure. The following search algorithm will be used to identify possible MACE:

- For cardiovascular death: any fatal case plus
    - Standardized MedDRA Queries (SMQ): Myocardial infarction (broad), Haemorrhagic central nervous system vascular conditions (narrow), Ischaemic Central Nervous System (CNS) Vascular conditions (narrow), Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (narrow), Embolic and thrombotic events (arterial, venous, vessel type unspecified and mixed arterial and venous) (narrow), Cardiac failure (broad), Shock-associated circulatory or cardiac conditions (excl torsades de pointes) (narrow), Torsade de pointes/QT prolongation (narrow), Arrhythmia related investigations, signs and symptoms (broad), Cardiomyopathy (broad), Supraventricular tachyarrhythmias (narrow), Ventricular tachyarrhythmias (narrow), Conduction defects (narrow)
    - All PTs under SOC of Cardiac disorders
    - [redacted]
- For non-fatal myocardial infarction: SMQ Myocardial infarction (broad)

- For non-fatal stroke: SMQ: Ischaemic Central Nervous System (CNS) Vascular conditions (narrow), Haemorrhagic central nervous system vascular conditions (narrow), Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (narrow)
- Congestive heart failure: SMQ Cardiac failure (broad)

Cardiovascular events will be tabulated only if 5 or more subjects have experienced a cardiovascular event. Cardiovascular events will be summarized by MedDRA SOC and PT in the MTX Analysis Set for the MTX Run-in Period and in the Safety Analysis Set for the pegloticase + MTX Period.

Cardiovascular events will also be reviewed by the Horizon internal safety review team.

Gout Flares

The number and percentage of subjects who experienced a gout flare (recorded in the AE eCRF), and number of gout flares per subject will be summarized for the MTX Run-in Period using the MTX Analysis Set. Percentages will be calculated using the number of subjects in the MTX Analysis Set. The number and percentage of subjects who experienced a gout flare and number of gout flares per subject during the Pegloticase + MTX Period (recorded in the AE eCRF) will be provided for the Safety Analysis Set. 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 48. Percentages will be based on the number of subjects who had follow-up at least as far as the start of the period-specific time period. For the full Pegloticase + MTX period, percentages will be calculated using the number of subjects in the Safety Analysis Set. Events are summarized for each period according to the onset date of the flare, and only summarized in the period of onset. In addition, events during the pegloticase + MTX period will be further summarized by month of occurrence, e.g., Month 1, Month 2, up to Month 12, where one month is defined as 30 days.

All AEs of special interest will also be listed.

14.4 Clinical Laboratory Evaluation

A local laboratory will be used for protocol-specified clinical laboratory parameters. Laboratory parameters (chemistry, hematology, and urinalysis) will be summarized in conventional units using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized for all continuous parameters. Summaries will be presented for change from methotrexate baseline (last assessment prior to the first dose of MTX in the MTX Run-in Period) and change from pegloticase baseline (last assessment prior to the first dose of pegloticase). The following laboratory parameters will be summarized:

- Hematology: hemoglobin, hematocrit, erythrocytes, leukocytes, neutrophils/leukocytes, lymphocytes/leukocytes, monocytes/leukocytes, eosinophils/leukocytes, basophils/leukocytes, platelets.

- Chemistry: albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, creatinine, glucose, sodium, potassium, calcium, chloride, total protein, blood urea nitrogen, hs-CRP.
- Urinalysis: albumin:creatinine ratio.

If a continuous laboratory value is reported as either below, above, below and equal or above and equal the limits of quantification, the qualifiers (>, >=, < or <=) 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").

Shift tables for laboratory parameters by Common Terminology Criteria for Adverse Events (CTCAE) grade will be presented by visit for those laboratory parameters with CTCAE v5.0 grade defined.

A summary of subjects with elevated liver function tests per specified criteria (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin) and subjects who possibly meet Hy's law criteria will also be provided by visit and overall. For the summary tables, all results collected within 30 days (inclusive) after the last dose of study treatment (MTX or pegloticase) will be included.

All laboratory tests will be listed, and results will be categorized as low, normal, or high based on their normal ranges. Separate listings of out-of-range results will also be presented.

14.5 Vital Signs

Vital signs (including heart rate, respiratory rate, systolic blood pressure and diastolic blood pressure) will be summarized using descriptive statistics at baseline and at each applicable post-baseline time point. Changes from baseline will also be summarized. During the MTX + pegloticase period, vitals will be measured pre-infusion and post-infusion. Weight will only be measured pre-infusion on Day 1 and Weeks 8, 16, 24, 36, at the non-infusion end of pegloticase infusions visit (if applicable) and at Week 48. For the summary tables, all results collected within 30 days (inclusive) after the last dose of study treatment (MTX or pegloticase) will be included.

14.6 Physical Examination

Physical examination results will be listed for each subject.

14.7 Electrocardiogram

An electrocardiogram (ECG) will be performed at Screening for all subjects and at the discretion of the investigator thereafter. The results will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated as clinically significant (CS) or not clinically significant (NCS) by the investigator. A summary of ECG results at Screening and a summary of any post-Screening results will be presented if data are available. All ECG results will be listed.

15. REFERENCES

Cole JC, Khanna D, Clements PJ, et al. Single-factor scoring validation for the Health Assessment Questionnaire-Disability Index (HAQ-DI) in patients with systemic sclerosis and comparison with early rheumatoid arthritis patients. Qual Life Res. 2006;15(8):1383-94.

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Woodworth T, Furst DE, Alten R, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: The Rheumatology Common Toxicity Criteria v2.0. J Rheumatol. 2007;34(6):1401-14.

16. APPENDICES

APPENDIX A: PRESENTATION OF DATA AND PROGRAMMING SPECIFICATIONS

Missing or incomplete dates

Medications

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

For partial start dates:

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

dose date, then the first dose date of MTX will be imputed. Otherwise, the first of the month will be used.

- If the year is provided and the month and day are missing and the year matches the year of the first pegloticase dose date and the year matches the year of the first MTX dose date, the month and day of the first MTX date will be imputed. Otherwise, if the year matches the year of the first dose of pegloticase, the first dose date of pegloticase will be imputed. Otherwise, if the year matches the year of the first MTX date, then the first dose date of MTX will be imputed. Otherwise, January will be used.
- If the start date is completely missing, the start date will not be imputed. If the stop date is after first dose date of pegloticase, the medication will be considered to be both prior, concomitant in the MTX Run-in Period, and concomitant in the Pegloticase + MTX Period. If the stop date is after the first dose date of MTX, but prior to the first dose date of pegloticase, the medication will be considered to be prior and concomitant in the MTX Run-in Period. If the stop date is prior to the first dose date of MTX, the medication will be considered to be prior only.
- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

For partial stop dates:

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

Adverse Events

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

For partial start dates:

- If the month and year of adverse event onset are provided but day is missing
    - If the month and year match the month and year of the first dose of MTX in the MTX Run-in Period AND match the month and year of the first infusion of pegloticase in the Pegloticase + MTX Period, the first dose date of MTX in the Run-in Period will be imputed and the event will be considered treatment emergent in the MTX Run-in Period and Pegloticase + MTX Period.
    - Otherwise, if the month and year match the month and the year of the first dose date of pegloticase, the day of the first infusion date of pegloticase will be imputed

and the AE will be considered treatment-emergent in the Pegloticase + MTX Period.

- Otherwise, if the month and year match the month and the year of the first dose date of MTX, the day of the first dose date of MTX will be imputed and the AE will be considered treatment-emergent in the MTX Run-in Period.
- Otherwise, the first of the month will be used and the treatment-emergent status will be assessed relative to the first infusion date of pegloticase and the first dose date of MTX.

- If the year of adverse event onset is provided, but the month and day are missing
  - If the year matches the year of the first dose of MTX in the MTX Run-in Period AND matches the year of the first infusion of pegloticase in the Pegloticase + MTX Period, the first dose date of MTX in the Run-in Period will be imputed and the event will be considered treatment emergent in the MTX Run-in Period and Pegloticase + MTX Period.
  - Otherwise, If the year matches the year of the first infusion date of pegloticase, the month and the day of the first infusion date of pegloticase will be imputed, and the AE will be considered treatment-emergent in the Pegloticase + MTX Period.
  - Otherwise, if the year matches the year of the first dose date of MTX, the month and day of the first dose of MTX will be imputed and the AE will be considered treatment-emergent in the MTX Run-in Period.
  - Otherwise, January 1st will be used and the treatment-emergent status will be assessed relative to the dosing start date of pegloticase and the first dose date of MTX.
- If the start date is completely missing, the AE will be considered treatment-emergent in the Pegloticase + MTX Period and the MTX Run-in Period, unless the stop date is complete or provides enough partial information to rule out a treatment-emergent status in the Treatment Period. This should be a rare occurrence.

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

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- **Days** – A duration expressed in days between 1 date (date1) and another later date (date2) is calculated using the formulas noted below:

  duration in days = date2 – date1 + 1

- **Height** – Height entries made in inches (in) are converted to centimeters (cm) using the following formula:
  height (cm) = height (in) × 2.54.
- **Weight** – Weight entries made in pounds (lb) are converted to kilograms (kg) using the following formula:
  weight (kg) = weight (lb)/2.2046.
- **Temperature** – Temperature entries in degrees Fahrenheit are converted to degrees centigrade using the following formula:
  temp (degrees centigrade) = 5/9 × [temp (degrees Fahrenheit) – 32].
- **Body Mass Index (BMI)** – BMI is calculated using height (cm) and weight (kg) using the following formula:
  BMI (kg/m^2) = weight (kg)/[[height (cm)/100]^2].
- **Change from baseline** – Change from baseline will be calculated as:
  Change = post-baseline value – baseline value.
- **Percent change from baseline** – Percent change from baseline will be calculated as:
  Percent change from baseline = (post-baseline value – baseline value)/baseline value × 100.

APPENDIX B: LIST OF TABLES, FIGURES AND LISTINGS

The following proposal for Sections 14 and 16.2 is completed according to ICH E3 guidelines. **Index of Section 14**

Table Number	Table Title	Analysis Set
14	**Tables and Figures Referred to but not Included in the Text**	
14.1	**Demographic Data**	
14.1.1	Analysis Sets and Disposition	All Subjects
14.1.2	Protocol Deviations	ITT Analysis Set
14.1.3.1	Demographic and Baseline Characteristics	ITT Analysis Set
14.1.3.2	Demographic and Baseline Characteristics	Safety Analysis Set
14.1.4.1	Gout History	ITT Analysis Set
14.1.4.2	Gout History	Safety Analysis Set
14.1.5	Medical History	ITT Analysis Set
14.1.6	Prior Medications by WHO Drug Dictionary ATC-4 Code and Preferred Name	MTX Analysis Set
14.1.7	Concomitant Medications During the Methotrexate Run-in Period by WHO Drug Dictionary ATC-4 Code and Preferred Name	MTX Analysis Set
14.1.8	Concomitant Medications During the Pegloticase + Methotrexate Period by WHO Drug Dictionary ATC-4 Code and Preferred Name	Safety Analysis Set
14.1.9	Subject Retention	ITT Analysis Set
14.2	**Efficacy Data**	
14.2.1.1	Serum Uric Acid < 6 mg/dL Responders during Month 6	ITT Analysis Set
14.2.1.2	Serum Uric Acid < 6 mg/dL Responders during Month 6	Per Protocol Analysis Set
14.2.1.3	Time to Pre-infusion Serum Uric Acid >= 6 mg/dL after Achieving sUA < 6mg/dL	ITT Analysis Set
14.2.1.4	Time to Pre-infusion Serum Uric Acid >= 6 mg/dL after Achieving sUA < 6mg/dL	Per Protocol
[redacted]		
14.2.5.1	Area Under the sUA Concentration Curve	ITT Analysis Set
[redacted]		

Table Number	Table Title	Analysis Set
[redacted]		
14.3	**Safety Data**	
14.3.1	**Displays of Adverse Events**	
14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events During the Methotrexate Run-in Period	MTX Analysis Set
14.3.1.2	Overall Summary of Treatment-Emergent Adverse Events During the Pegloticase + Methotrexate Period	Safety Analysis Set
14.3.1.3.1	Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Methotrexate Run-in Period	MTX Analysis Set
14.3.1.3.2	Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Pegloticase + Methotrexate Period	Safety Analysis Set
14.3.1.3.3	Incidence of Treatment-Emergent Adverse Events by Preferred Term During the Pegloticase + Methotrexate Period	Safety Analysis Set
14.3.1.4.1	Incidence of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to Methotrexate During the Methotrexate Run-in Period	MTX Analysis Set
14.3.1.4.2	Incidence of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to Methotrexate During the Pegloticase + Methotrexate Period	Safety Analysis Set
14.3.1.4.3	Incidence of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to Pegloticase During the Pegloticase + Methotrexate Period	Safety Analysis Set
14.3.1.5.1	Incidence of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity During the Methotrexate Run-in Period	MTX Analysis Set
14.3.1.5.2	Incidence of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity During the Pegloticase + Methotrexate Period	Safety Analysis Set
14.3.1.6.1	Incidence of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term During the Methotrexate Run-in Period	MTX Analysis Set
14.3.1.6.2	Incidence of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term During the Pegloticase + Methotrexate Period	Safety Analysis Set
14.3.1.7.1	Incidence of Treatment-Emergent Adverse Events Leading to Methotrexate Treatment Discontinuation by System Organ Class and Preferred Term During the Methotrexate Run-in Period	MTX Analysis Set

Table Number	Table Title	Analysis Set
14.3.1.7.2	Incidence of Treatment-Emergent Adverse Events Leading to Methotrexate Treatment Discontinuation by System Organ Class and Preferred Term During the Pegloticase + Methotrexate Period	Safety Analysis Set
14.3.1.8	Incidence of Treatment-Emergent Adverse Events Leading to Pegloticase Treatment Discontinuation by System Organ Class and Preferred Term During the Pegloticase + Methotrexate Period	Safety Analysis Set
14.3.1.9.1	Incidence of Treatment-Emergent Adverse Events Related to COVID-19 by System Organ Class and Preferred Term During the Methotrexate Run-in Period	MTX Analysis Set
14.3.1.9.2	Incidence of Treatment-Emergent Adverse Events Related to COVID-19 by System Organ Class and Preferred Term During the Pegloticase + Methotrexate Period	Safety Analysis Set
14.3.1.10.1	Treatment-Emergent Adverse Events of Special Interest during the Pegloticase + MTX Period: Infusion Reactions and Anaphylactic Reactions Reported by the Investigator by Maximum Severity and Time Relative to Most Recent Pegloticase Infusion	Safety Analysis Set
14.3.1.10.2.1	Treatment-Emergent Adverse Events of Special Interest during the Pegloticase + MTX Period: Incidence of Infusion Reactions and Anaphylactic Reactions Reported by the Investigator by Baseline Anti-PEG Antibody Status and Maximum Severity	Safety Analysis Set
14.3.1.10.2.2	Treatment-Emergent Adverse Events of Special Interest during the Pegloticase + MTX Period: Incidence of Infusion Reactions and Anaphylactic Reactions Reported by the Investigator by Anti-PEG ADA Status Post-baseline and Maximum Severity	Safety Analysis Set
14.3.1.10.3.1	Treatment-Emergent Adverse Events of Special Interest during the Pegloticase + MTX Period: Incidence of Infusion Reactions and Anaphylactic Reactions Reported by the Investigator by Baseline Anti-uricase Antibody Status and Maximum Severity	Safety Analysis Set
14.3.1.10.3.2	Treatment-Emergent Adverse Events of Special Interest during the Pegloticase + MTX Period: Incidence of Infusion Reactions and Anaphylactic Reactions Reported by the Investigator by Anti-uricase ADA Status Post-baseline and Maximum Severity	Safety Analysis Set
14.3.1.11.1	Treatment-Emergent Adverse Events of Special Interest during the Methotrexate Run-in Period: Cardiovascular Events Reported by the Investigator	MTX Analysis Set
14.3.1.11.2	Treatment-Emergent Adverse Events of Special Interest during the Pegloticase + MTX Period: Cardiovascular Events Reported by the Investigator	Safety Analysis Set
14.3.1.12.1	Treatment-Emergent Adverse Events of Special Interest during the Methotrexate Run-in Period: Gout Flares	MTX Analysis Set
14.3.1.12.2	Treatment-Emergent Adverse Events of Special Interest during the Pegloticase + MTX Period: Gout Flares	Safety Analysis Set
14.3.4.1.1.1	Change from Methotrexate Baseline to Each Post-baseline Visit in Hematology Parameters	Safety Analysis Set
14.3.4.1.1.2	Change from Pegloticase Baseline to Each Post-baseline Visit in Hematology Parameters	Safety Analysis Set

Table Number	Table Title	Analysis Set
14.3.4.1.1.3	Shift Summary of Hematology Results from Methotrexate Baseline by CTCAE Grade	Safety Analysis Set
14.3.4.1.1.4	Shift Summary of Hematology Results from Pegloticase Baseline by CTCAE Grade	Safety Analysis Set
14.3.4.1.2.1	Change from Methotrexate Baseline to Each Post-baseline Visit in Chemistry Parameters	Safety Analysis Set
14.3.4.1.2.2	Change from Pegloticase Baseline to Each Post-baseline Visit in Chemistry Parameters	Safety Analysis Set
14.3.4.1.2.3	Shift Summary of Chemistry Results from Methotrexate Baseline by CTCAE Grade	Safety Analysis Set
14.3.4.1.2.4	Shift Summary of Chemistry Results from Pegloticase Baseline by CTCAE Grade	Safety Analysis Set
14.3.4.1.3	Change from Pegloticase Baseline to Each Post-baseline Visit in Continuous Urinalysis Parameters	Safety Analysis Set
14.3.4.1.4	Number and Percentage of Subjects with Elevated Liver Function Test Results by Visit	Safety Analysis Set
14.3.4.2	Change from Baseline to Each Post-baseline Visit in Vital Sign Parameters	Safety Analysis Set
14.3.4.3.1	Summary of Electrocardiograms at Screening	Safety Analysis Set
14.3.4.3.2	Summary of Post-screening Electrocardiograms	Safety Analysis Set
14.3.4.4.1.1	Incidence of Serum Anti-PEG IgG Antibody Results	ITT Analysis Set
14.3.4.4.1.2	Incidence of Serum Anti-uricase IgG Antibody Results	ITT Analysis Set
14.3.4.4.2.1	Descriptive Statistics for Serum Pegloticase Concentrations	PK Analysis Set
14.3.4.4.2.2	Descriptive Statistics for Serum Pegloticase Concentrations by Baseline Anti-PEG ADA Status	PK Analysis Set
14.3.4.4.2.3	Descriptive Statistics for Serum Pegloticase Pharmacokinetic Parameters	PK Analysis Set
14.3.4.4.2.4	Descriptive Statistics for Serum Pegloticase Pharmacokinetic Parameters by Baseline Anti-PEG ADA Status	PK Analysis Set
[redacted]	[redacted]	[redacted]
14.3.4.5.1	Extent of Methotrexate Exposure	MTX Analysis Set
14.3.4.5.2	Extent of Pegloticase Exposure in the Pegloticase + MTX Period	Safety Analysis Set
Figures		
14.2.1.1	Mean Pre-Infusion Serum Uric Acid (mg/dL) by Visit	ITT Analysis Set
14.2.1.2	By Subject Plot of Serum Uric Acid (mg/dL) by Visit	ITT Analysis Set
14.2.1.3	Kaplan-Meier Curve for Time to Pre-infusion Serum Uric Acid ≥ 6 mg/dL from Day 1 to Week 24	ITT Analysis Set
14.2.1.4	Kaplan-Meier Curve for Time to Two Consecutive Serum Uric Acid ≥ 6 mg/dL	ITT Analysis Set
14.3.4.1	Mean Serum Pegloticase Concentrations (µg/mL) by Time for Cycle 1	PK Analysis Set

Index of Section 16.2

Listing Number	Listing Title
16.2.6.5.2	Serum Pegloticase Pharmacokinetic Parameters
16.2.6.5.3	Intervals (Hours) Used for Determination of Serum Pegloticase Lambda z Values
16.2.6.6	Antibody Results
[redacted]	
16.2.7	**Adverse Events Listings**
16.2.7.1	Adverse Events
16.2.7.2	Serious Adverse Events
16.2.7.3	Adverse Events Leading to Death
16.2.7.4.1	Adverse Events Leading to Permanent Withdrawal of Methotrexate
16.2.7.4.2	Adverse Events Leading to Permanent Withdrawal of Pegloticase
16.2.7.5	Adverse Events of Special Interest: Cardiovascular Events
16.2.7.6	Adverse Events of Special Interest: Symptoms Related to Infusion Reaction or Anaphylactic Reactions
16.2.7.7	Adverse Events of Special Interest: Gout Flares
16.2.8.1	**Listing of Individual Laboratory Measurements by Subject**
16.2.8.1.1	Clinical Laboratory Hematology Test Results
16.2.8.1.2	Clinical Laboratory Chemistry Test Results
16.2.8.1.3	Clinical Laboratory Urinalysis Test Results
16.2.8.1.4	Clinical Laboratory G6PD Test Results at Screening
16.2.8.1.5.1	Clinical Laboratory Hematology Test Results Outside of Normal Range
16.2.8.1.5.2	Clinical Laboratory Chemistry Test Results Outside of Normal Range
16.2.8.1.5.3	Clinical Laboratory Urinalysis Test Results Outside of Normal Range
16.2.8.1.6	Pregnancy Test Results
16.2.8.2	**Other Data**
16.2.8.2.1	Vital Signs
16.2.8.2.2	12-lead ECG Results
16.2.8.2.3	Physical Examination
16.2.8.2.4	Principal Investigator Assessment of Subject Clinical Status and Treatment Goals

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