Statistical Analysis Plan

Horizon Therapeutics Ireland DAC

HZNP-KRY-407

A Phase 4, Multicenter, Open-label, Efficacy and Safety Trial of Pegloticase and Methotrexate Co-administered in Patients with Uncontrolled Gout who have Previously Received Pegloticase Monotherapy but did not Maintain a Serum Uric Acid Response (ADVANCE)

Protocol Version: Version 2.0

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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.

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LIST OF ABBREVIATIONS

Abbreviation	Full Notation
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
BLQ	Below limit of quantification
BMI	Body mass index
CI	Confidence interval
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
DECT	Dual-energy computed tomography
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	estimated glomerular filtration rate
ET	Early termination
CCI	[redacted]
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
hs-CRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
CCI	[redacted]
IR	Infusion reaction
ITT	Intent-to-treat
IV	Intravenously
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MCS	Mental composite summary
MTX	Methotrexate
NCS	Not clinically significant
PCS	Physical composite summary

Abbreviation	Full Notation
CCI	CCI
CCI	
CCI	
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
CCI	CCI
SMQ	Standard MedDRA query
SOC	System organ class
sUA	Serum uric acid
TLFs	Tables, listings, and figures
VAS	Visual analog scale

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-407 [A Phase 4, Multicenter, Open-label, Efficacy and Safety Trial of Pegloticase and Methotrexate Co-administered in Patients with Uncontrolled Gout who have Previously Received Pegloticase Monotherapy but did not Maintain a Serum Uric Acid Response (ADVANCE)]. 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 2.0, 10 AUG 2021
- Annotated electronic case report form (eCRF), Version 1.054, 29 JAN 2021

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to demonstrate that 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, is greater than 20% in subjects receiving pegloticase with methotrexate (MTX).

3.2 Secondary Objectives

To evaluate the effect of pegloticase with MTX on the following:

- 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.
- The proportion of subjects who experienced any of the following events from Day 1 to Week 24: infusion reaction (IR) leading to discontinuation of treatment, anaphylaxis or meeting Individual Subject sUA Discontinuation Criteria.
- The change from Baseline in urate deposition volume, measured by dual-energy computed tomography (DECT) scan.
- The change from Baseline in Health Assessment Questionnaire (HAQ) - Disability Index (HAQ-DI) score.
- The change from Baseline in HAQ pain score.
- The change from Baseline in HAQ health score.

3.3 Exploratory Objectives

To evaluate the effect of pegloticase with MTX on the following:

3.4 Safety and Tolerability Objectives

To evaluate the effect of pegloticase with MTX on the following:

- The adverse event (AE)/serious adverse event (SAE) profile overall for pegloticase and MTX and the incidence of adverse events of special interest (AESIs), including IRs, anaphylaxis, gout flares and major adverse cardiovascular events (MACE, defined as non-fatal stroke, non-fatal myocardial infarction, cardiovascular death and congestive heart failure).
- The change from Baseline in safety laboratory test results, including high-sensitivity C-reactive protein (hs-CRP).
- The change from Baseline in vital signs.

4. STUDY DESIGN AND PLAN

This is a Phase 4, multicenter, open-label trial of pegloticase with MTX in adult subjects with uncontrolled gout who were previously treated with pegloticase without a concomitant

immunomodulator and stopped pegloticase due to failure to maintain sUA response and/or a clinically mild IR. Approximately 30 subjects will be enrolled. The treatment period with pegloticase + MTX will be approximately 24 weeks, with optional extension up to 48 weeks.

The trial design will include 5 distinct components:

1) a Screening Period, lasting up to 42 days;
2) a 6-week MTX Tolerability Assessment Period (hereafter referred to as the MTX Run-in Period);
3) a 24-week Pegloticase + MTX Treatment Period, which will include a Week 24/End of Trial/Early Termination Visit (subjects that end MTX and pegloticase treatment prior to Week 24 will remain on trial for follow-up until the Week 24 visit);
4) an Optional Pegloticase + MTX Extension Period from Week 24 to Week 48, if a subject may gain further benefit with additional pegloticase treatment per the discretion of the Principal Investigator, which will include a Week 48/Optional End of Trial/Optional Early Termination Visit and
5) a 30-day post-treatment follow-up (phone/email) 30 days after the last pegloticase infusion or last dose of MTX (for subjects who are unable to tolerate MTX during the MTX Run-in Period and do not dose pegloticase.) Subjects that end MTX and pegloticase treatment prior to Week 24 and remain on trial for at least 30 days prior to Week 24 will complete the 30-day Post-Treatment Follow-up as part of the visits following the End of Pegloticase visit.

All subjects who meet eligibility criteria at Screening will begin titrating up to a once weekly subcutaneous MTX at a target dose of 25 mg (if estimated glomerular filtration rate (eGFR) is ≥45 mL/min/1.73 m^2) or 15 mg (if eGFR is ≥30 and <45 mL/min/1.73 m^2) for 6 weeks prior to the first dose of pegloticase. Subjects will also take folic acid at a starting dose of 1 mg orally every day beginning at Week -6 (preferably 2 days prior to the first dose of MTX) continuing until prior to the End of Pegloticase Visit (if applicable) or until 1 week after the last pegloticase infusion for subjects who have not stopped pegloticase treatment. A higher folic acid dose or an alternative folate supplement will be allowed.

Subjects must be able to tolerate MTX at a minimum dose of 15 mg during the 6-week MTX run-in period to be eligible to participate in the Pegloticase + MTX Treatment Period, regardless of baseline eGFR. Subjects who are unable to tolerate MTX 15 mg during the MTX run-in period will be considered MTX run-in screen failures.

All subjects who meet the inclusion/exclusion criteria and complete the MTX run-in period will be considered enrolled subjects and will receive the first pegloticase infusion on Day 1. All subsequent doses and trial visits will be scheduled based on the Day 1 visit date. During the Pegloticase + MTX Treatment Period, pegloticase 8 mg will be administered intravenously (IV) every 2 weeks from Day 1 through the Week 22/Week 46 visit, after all predose trial visit

assessments have been completed at each visit. The date, start and stop time of infusion will be recorded.

Individual subject sUA will be measured locally within 48 hours prior to each pegloticase infusion throughout the trial and by the central laboratory on infusion visit days. In addition, sUA will be collected between infusions for the first 12 weeks of the trial. These interim sUA values will be measured at the 1st (~24 hours), 4th (~96 hours), 7th (~168 hours) and 10th (~240 hours) day after each infusion at Day1, Week 2, Week 4, Week 6 and at the 1st (~24 hours) and 7th (~168 hours) day after infusion at Week 8, Week 10, and Week 12.

Pegloticase treatment will continue if there is a meaningful sUA reduction from the Baseline, at the discretion of the Principal Investigator, even if sUA<6 mg/dL is not maintained consistently over the 2-week interval between infusions during this 12-week period. However, pegloticase treatment should be stopped if the lowest available interim sUA value (typically the 1st day [~24 hours] after infusion) after the pegloticase infusion at Week 2, 4, 6, 8, 10 or 12 is less than a 50% reduction from the highest sUA value measured between Screening and pre-infusion on Day 1.

Prior to Week 22, subjects who discontinue treatment due to individual subject sUA levels, as evaluated by the Principal Investigator, will remain in the trial for biweekly visits, including the Week 24/End of Trial/Early Termination and 30-Day Post-Treatment Follow-up Visits if not captured as part of post treatment follow-up.

Two sequential cohorts of subjects will be enrolled in this trial. Cohort 1 is targeted to enroll 10 subjects who previously failed to maintain sUA response with pegloticase monotherapy and stopped pegloticase treatment without a history of pegloticase-related IR. After 7 and 10 subjects in Cohort 1 complete at least 6 infusion visits, safety assessments of IR and anaphylaxis from available subjects' data will be performed by the Safety Review Team (comprising members of the Horizon Clinical Development and Patient Safety and Pharmacovigilance Teams) based on pre-determined tolerability criteria. If a subject discontinues treatment or discontinues the trial prior to the 7th infusion, their available data will be included in the safety assessment. If the safety assessment during Cohort 1 indicates that the pegloticase infusions are well tolerated based on the pre-determined tolerability criteria (no more than one-third of subjects experience a severe IR and/or anaphylaxis) then the trial can begin enrolling Cohort 2. If the safety assessment indicates that the pegloticase infusions are not well tolerated based on the predetermined tolerability criteria, then the trial will cease to screen and enroll new subjects. Subjects who are ongoing and benefitting from continued treatment, as determined by the Principal Investigator at the time of the termination of new subject screenings, will be permitted to continue treatment and trial visits.

The aim is to enroll up to 20 subjects with or without a history of pegloticase-related clinically mild IR in Cohort 2. After 3, 6, 10, 15 and 20 subjects in Cohort 2 complete at least 6 infusion visits, safety assessments of IR and anaphylaxis from available subjects' data will be performed by the Safety Review Team. If the safety assessment indicates that the pegloticase infusions are

not well tolerated based on the pre-determined tolerability criteria or in the absence of subjects with a history of pegloticase-related clinically mild IR, the trial will continue enrolling subjects without a history of pegloticase-related clinically mild IR to reach a total of 30 subjects enrolled for the trial.

Depending on any potential safety signals reported (e.g., serious IR or any SAE related to pegloticase infusion), regular quarterly and/or ad hoc safety assessments will be conducted during the trial as specified in the Safety Management Plan and the Safety Review Team Charter. The regular quarterly reviews will include review of the database by the Safety Review Team and will be conducted as set out in the Safety Management Plan. The first safety review meeting will occur approximately after the first 3 subjects in Cohort 1 complete at least 12 weeks of the Pegloticase + MTX Treatment period (6 infusion visits). The Safety Review Team could stop the trial for other significant safety reasons.

If 3 events of anaphylaxis (as assessed by PI) occur, an Adjudication Committee (composed of independent experts external to Horizon) will be established for this trial to adjudicate the AESI Anaphylaxis at a frequency defined in the Adjudication Committee Charter. The AESI of IR, MACE and gout flare will not be adjudicated.

Samples for measurement of sUA levels will be collected at Screening, during the MTX run-in period, pre- each infusion, post-infusion on Day 1 and at the Week 10, 12, 14, 20, 22, 32, 34, 44 and 46 Visits and on non-infusion days on the 1st (~24 hours), 4th (~96 hours), 7th (~168 hours) and 10th (~240 hours) day after the first 4 infusions (Infusions 1, 2, 3, 4) and on the 1st (~24 hours) and the 7th (~168 hours) day after the 5th , 6th and 7th infusion, Weeks 21 and 23, and at the End of Pegloticase (if applicable) or the Week 24 or 48/End of Trial/Early Termination Visit.

Samples will be collected for CCI [redacted] and CCI [redacted]. 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 and urine test, will be performed.

All sites and subjects will be provided with FDA-approved handheld sUA devices to measure subject uric acid levels based on capillary samples. Results will be collected in the eCRF at non-infusion visits and pre- and post-infusion during pegloticase infusion visits. Subjects may also use the device to measure uric acid at home. Results will be collected for exploratory uses only. No in-trial treatment decisions will be made based upon the data generated with the handheld device.

5. DETERMINATION OF SAMPLE SIZE

A sample size of 30 subjects is planned for this trial to provide a sizeable number of subjects to support the following projections. The primary efficacy endpoint will be demonstrated to be statistically greater than 20% if at least 12/30 (40%) responders are observed. In that case, the

lower bound of a 95% confidence interval (CI) for the proportion of responders will be approximately 23%.

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 and with an overall column. If Cohort 2 enrolls both subjects with previous mild IR and those with no previous IR, then the data will be summarized by IR category (no IR, mild IR) within Cohort 2 and for Cohorts 1 and 2 no IR subjects combined.

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, Table 7, and Table 8 below. If 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, chemistry, and urinalysis clinical laboratory assessments. Table 3 shows the windows for the hsCRP laboratory assessments. Table 4 shows the windows for the DECT scans. Table 5 shows the windows for HAQ and CCI count assessments. Table 6 shows the windows for CCI [redacted], and CCI [redacted]. Table 7 shows the windows for CCI [redacted] and CCI [redacted] assessments. Table 8 shows the windows for sUA assessments. Unscheduled sUA visits, assessed by the central or local laboratory, will also be assigned to an analysis visit according to the windows in Table 8. These unscheduled assessments will only be used for the determination of sUA responder status. 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 2	15	2 – 22
	Week 4	29	23 – 36
	Week 6	43	37 – 50
	Week 8	57	51 – 64
	Week 10	71	65 – 78
	Week 12	85	79 – 92
	Week 14	99	93 – 106
	Week 16	113	107 – 120
	Week 18	127	121 – 134
	Week 20	141	135 – 148
	Week 22	155	149 – 162
	Week 24	169	163 – 176
	Week 26	183	177 – 190
	Week 28	197	191 – 204
	Week 30	211	205 – 218
	Week 32	225	219 – 232
	Week 34	239	233 – 246
	Week 36	253	247 – 260
	Week 38	267	261 – 274
	Week 40	281	275 – 288
	Week 42	295	289 – 302
	Week 44	309	303 – 316
	Week 46	323	317 – 330

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
	Week 48	337	≥331

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

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 2	15	2 – 29
	Week 6	43	30 – 71
	Week 14	99	72 – 134
	Week 24	169	135 – 211
	Week 36	253	212 - 295
	Week 48	337	≥296

Table 3: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (hsCRP)

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 14	99	2 – 134
	Week 24	169	135 – 211
	Week 36	253	212 – 295
	Week 48	337	≥296

Table 4: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (DECT)

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 14	99	2 – 134
	Week 24	169	135 – 253
	Week 48	337	≥254

Table 5: Visit Windows for Assigning ET and End of Pegloticase Visits to a Scheduled Visit (HAQ, CCI)

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 6	43	2 – 71
	Week 14	99	72 – 120
	Week 20	141	121 – 155
	Week 24	169	156 – 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 (CCI , CCI)

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
	Week 14	99	2 – 134
	Week 24	169	135 – 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 (CCI , CCI)

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit (days)
Pegloticase + MTX	Day 1	1	1
	Week 2	15	2 – 29
	Week 6	43	30 – 71
	Week 14	99	72 – 127
	Week 22	155	128 – 162
	Week 24	169	163 – 211
	Week 36	253	212 – 295
	Week 48	337	≥296

Table 8: 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 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
	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

8. ANALYSIS SETS

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

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

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

- The intent-to-treat (ITT) analysis set will include all enrolled subjects who receive at least 1 dose of pegloticase + MTX.

The following analysis set will be used for[redacted]

- [redacted].

Note that the safety analysis set and ITT analysis set are defined the same for this protocol.

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 -6) 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 an incorrect dose;
- Subjects who received an excluded concomitant treatment.

The number of subjects experiencing any minor protocol deviation, any major protocol deviation and any deviation related to COVID-19, along with the number of protocol deviations, will be

presented for subjects in the ITT analysis set. Major protocol deviations will be further summarized by deviation category.

All protocol deviations, including the deviation designation (major or minor), category, subcategory, and indication of whether the deviation was related to COVID-19 will be presented in a data listing.

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.

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), and substance use history.

Descriptive statistics will be presented for age, height, weight, BMI, sex, ethnicity, race, childbearing potential (for females only), tobacco use, alcohol use, and other substance use. Demographic and baseline characteristics will be summarized for the ITT analysis set.

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, 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, kidney function impacted by gout, number of episodes of renal colic in the past year, 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 for the ITT analysis set.

Medical/Surgical history

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

Medical/surgical history will be summarized in the ITT analysis set and will be ordered alphabetically by system organ class (SOC) and by preferred term (PT) within system organ class.

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

Pegloticase History

Pegloticase use history will be summarized in the ITT analysis set using descriptive statistics. Pegloticase history variables will include: time since last dose to screening, duration of treatment, dosing frequency, total number of infusions, reason for stopping pegloticase treatment, sUA stopping rule met (if applicable), and infusion reaction severity (if applicable).

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.

Concomitant procedures and prior and concomitant medications will be presented in a listing.

10. EFFICACY ANALYSES

The ITT analysis set will be used to assess efficacy endpoints. The estimand for the primary analysis will use the Treatment Policy Strategy (data will be used regardless of whether an intercurrent event occurred) for most intercurrent events; the intercurrent event of treatment or study discontinuation related to COVID-19 (leading to data that are missing completely at random) will be addressed with a While-on Treatment Strategy (only values prior to occurrence of intercurrent event will be used).

10.1 Efficacy Variables

10.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the 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, pre and post infusion results at Week 22, results at 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.

10.1.2 Secondary Efficacy Endpoints

- Month 3 responder rate – defined as the proportion of subjects achieving and maintaining sUA < 6 mg/dL for at least 80% of the time during Month 3. The Month 3 responder rate will consider pre and post infusion results at Week 10, Week 12, and Week 14 and also

the between-visit non-infusion results at ~24 hours and ~168 hours after doses at Week 10 and 12.

- The proportion of subjects who experienced any of the following events from Day 1 to Week 24: IR leading to discontinuation of treatment, anaphylaxis or meeting Individual Subject sUA Discontinuation Criteria (defined as the lowest available interim sUA value after the pegloticase infusion at Week 2, 4, 6, 8, 10 or 12 is less than a 50% reduction from the highest sUA value measured between Screening and pre-infusion on Day 1).
- The change from Baseline in urate deposition volume, measured by dual-energy computed tomography (DECT) scan. The DECT will include, at a minimum, hands, feet and knees and other anatomical areas as clinically indicated.
- Change from baseline to each postbaseline assessment in HAQ-DI score. The HAQ-DI assesses the subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip and usual activities [Cole, 2006]. The subject's ability to accomplish each activity in the past week is indicated as: without any difficulty, with some difficulty, with much difficulty and unable to do. Any devices that are usually used to complete activities and any categories for which help from another person is needed is also assessed. See details on scoring of HAQ-DI in Appendix A.
- Change from baseline to each postbaseline assessment in HAQ Pain Score. The HAQ Pain question asks, "How much pain have you had in the past week?" on a scale of 0-100 where 0 represents no pain and 100 represents severe pain.
- Change from baseline to each postbaseline assessment in HAQ Health score. The HAQ Health question asks, "Please rate how well you are doing on a scale of 0 to 100 (0 represents 'very well' and 100 represents 'very poor' health)".

10.1.3 Exploratory Efficacy Endpoints

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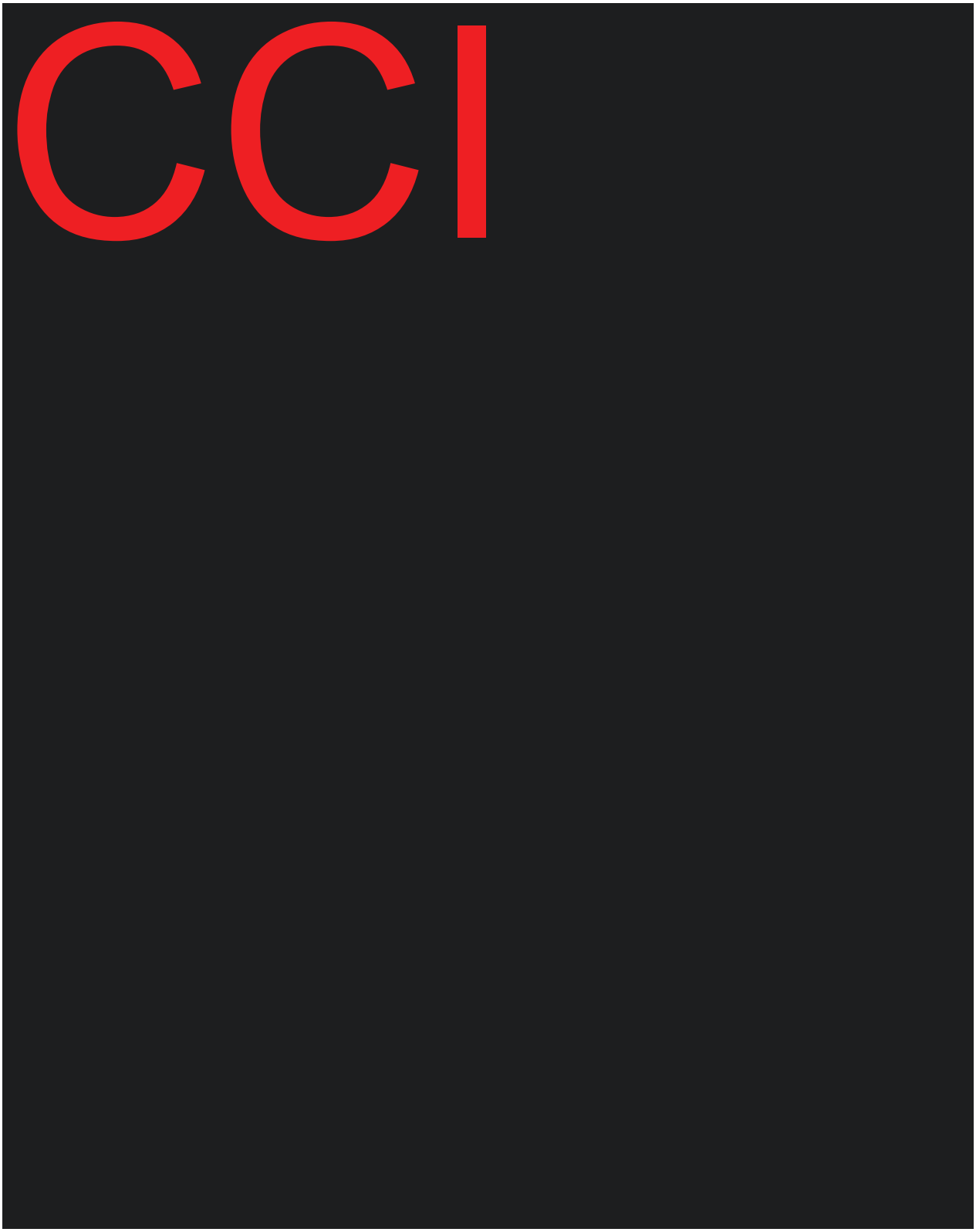
CCI

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. 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.

Safety data will be summarized for safety assessments conducted after 7 and 10 subjects in Cohort 1 complete 6 infusions and after 3, 6, 10, 15 and 20 subjects in Cohort 2 complete 6 infusions. The results of these analyses will determine if enrollment will continue in each cohort. Efficacy and safety data may be summarized periodically throughout the trial to support scientific publications. Additionally, safety data will be summarized regularly for safety monitoring. Final analysis will occur when all subjects have completed the trial. No Type 1 error rate adjustments will be made due to multiple summaries.

10.6 Examination of Subgroups

No subgroup analysis is planned for this study.

10.7 Multiple Comparison/Multiplicity

No Type 1 error rate adjustments will be made due to multiple comparisons.

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 at the Screening, Week -6 (prior to the first dose of MTX) and Week -2 Visits. On Day 1, a pre- and post-infusion sUA will be collected to be shipped to the central laboratory. For the remainder of trial visits beginning at Week 2 during the Pegloticase + MTX Treatment Period, 2 sUA samples will be collected within 48 hours prior to each pegloticase infusion. One sample will be for sUA testing at the site's local laboratory and the second sample will be sent to the central laboratory (the central laboratory sample may be drawn separately from the local collection). Additional serum samples for sUA levels will be collected after the end of each pegloticase infusion prior to discharge at Weeks 10, 12, 14, 20, 22, 32, 34, 44 and 46. Single serum samples for measurement of sUA will also be collected at non-infusion visits at Weeks 21 and 23 and at the End of Pegloticase (if applicable) or the Week 24 or 48/End of Trial/ET Visit. Serum for sUA analysis will also be collected at Day 1 (~24 hours) post-infusion, Day 4 (~96 hours) post-infusion, Day 7 (~168 hours) post-infusion, and Day 10 (~ 240 hours) post-infusion following the first 4 pegloticase infusions at Day 1, Weeks 2, 4, 6. , Serum for sUA analysis will also be collected at Day 1 (~24 hours) post-infusion, and Day 7 (~168 hours) post-infusion following the Week 8, 10 and 12 infusions. If infusion intervals of less than 2 weeks should occur due to scheduling issues, the 1st day (~24hours) samples must be obtained at a minimum and also the 7th day (~168 hours) if feasible.

Prior to Week 22, subjects whose lowest available interim sUA value (typically the 1st day [~24 hours] after infusion) after the pegloticase infusion at Week 2, 4, 6, 8, 10 or 12 is less than a 50%

reduction from the highest sUA value measured between Screening and pre-infusion on Day 1 will discontinue treatment and complete the End of Pegloticase Visit within 2 weeks of the last infusion, but remain in the trial for biweekly visits, including the Week 24/End of Trial/Early Termination and 30-Day Post-Treatment Follow-up Visits.

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

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 at the same time point, is available.

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

11.2 Primary Efficacy Endpoint and Analysis

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 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.

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CCI [redacted]

[redacted]

[redacted] CCI [redacted]

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 individual subject sUA discontinuation criteria or discontinues pegloticase with reason of 'Lack of Efficacy', prior to Week 24 will be counted as a non-responder.

For subjects who postponed or missed visits due to COVID-19, only visits occurring prior to any disruption of treatment (> 21 days between infusions) or cessation in treatment will be used for the primary analysis. Any results following the disruption in treatment will be set to missing. Subjects with disrupted treatment due to COVID-19 at any point prior to the Month 6 period will not be included in the primary analysis.

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 the analysis period, subjects with only one measurement above the cutoff in the analysis period, and subjects with only one measurement below the cutoff in the analysis period will be summarized.

11.3 Additional Analyses of sUA

The proportion of time sUA < 6 mg/dL between first infusion and Week 24 will be calculated similarly to the primary endpoint but based on all available sUA values (from central and local labs (if central unavailable)) collected between the first infusion and Week 24. The proportion of time will be summarized with descriptive statistics by Month 6 responder groups (non-responders vs. responders).

The Month 3 responder rate will be summarized similar to Month 6 responder rates described above. The Month 3 responder rate will consider pre and post infusion results at Week 10, Week 12, and Week 14 and also the between-visit non-infusion results at ~24 hours and ~168 hours after doses at Week 10 and 12. The number and proportion of responders along with the two-sided 95% exact Clopper-Pearson CIs for the responder rates will be presented. The proportion of hours during Month 3 where the sUA < 6 mg/dL will be summarized using descriptive statistics.

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. A two-sided 95% Wald CI will be presented for the mean observed value and mean change from baseline for each visit. The proportion of subjects with sUA < 6 mg/dL at each scheduled time point will be summarized, along with the two-sided 95% exact Clopper-Pearson CIs.

Line plots of the observed mean pre-infusion sUA values at each scheduled visit will be presented by cohort and Cohort 1 and 2 combined. By-subject plots of sUA values by time will also be presented and will include a reference line at 6 mg/dL.

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11.4 Analyses of Proportion of Subjects with Infusion Reactions, Anaphylaxis, and Meeting Individual Subject sUA Discontinuation Criteria

The proportion of subjects who experience an IR leading to pegloticase discontinuation, anaphylaxis, or meet individual subject sUA discontinuation criteria will be presented along with the two-sided 95% exact Clopper-Pearson CIs. The proportion of subjects meeting each criteria separately will also be presented.

11.5 Analyses of DECT Scans

The observed values and the change from baseline for urate deposition volume, hand erosion score, foot erosion score, and total bone erosion score at each scheduled time point will be summarized using descriptive statistics. A two-sided 95% Wald CI for the changes from baseline will be presented. CCI

11.6 CCI

CCI

CCI [redacted]

11.7 Analyses of Health Assessment Questionnaire

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. A two-sided 95% Wald CI for the changes from baseline will be presented.

11.8 Analyses of CCI [redacted]

CCI [redacted]

11.9 Analyses of CCI [redacted]

CCI [redacted]

11.10 Analyses of CCI [redacted]

CCI [redacted]

11.11 Analyses of CCI [redacted]

CCI [redacted]

11.12 Analyses of CCI [redacted]

CCI [redacted]

11.13 Analyses of CCI

Subjects will be assessed for the presence of CCI . The number of CCI will be recorded for the CCI

For subjects with CCI at baseline, the mean number of CCI and change from baseline will be presented by visit. A two-sided 95% CCI for the changes from baseline will be presented.

12. CCI

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-

CCI

CCI

12.3 CCI

CCI

13. CCI

-
-

- CCI [redacted]
- [redacted]

[redacted]

[redacted]

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 Treatment Period and Optional Pegloticase + MTX Extension 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, total dosage received, and average doses received.

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

- Duration of treatment defined as the last dose of MTX prior to the Day 1 visit date – first dose date of MTX + 1
- Total MTX dosage (prescribed dose) 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 any dose reduction (reduction in prescribed dose for reason of abnormal labs, AE, or titration down).

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

- Separately for the Pegloticase + MTX Treatment Period, Optional Pegloticase + MTX Extension Period, and overall
    - Number of pegloticase infusions received
    - Duration in days between first and last pegloticase infusion in the given period, 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
  - Number of subjects not receiving MTX between previous infusion and current infusion
- MTX
  - Duration of MTX dosing during the Pegloticase + MTX Treatment Period, defined as the last MTX date prior to Week 24 – first MTX dosing date (on or after the date of the Day 1 visit) + 1
  - Total MTX dosage (in mg) received during the Pegloticase + MTX Treatment period
  - Average MTX dose (in mg) (total dosage for the Pegloticase + MTX Treatment Period divided by number of doses taken during the Pegloticase + MTX Treatment Period)
  - Number of subjects with any dose reduction (reduction in prescribed dose for reason of abnormal labs, AE, or titration down) in the Pegloticase + MTX Treatment Period.
  - Duration of MTX dosing during the Optional Pegloticase + MTX Extension Period, defined as the last MTX date – Week 24 MTX dosing date + 1
  - Total MTX dosage (in mg) received during the Optional Pegloticase + MTX Extension period
  - Average MTX dose (in mg) (total dosage for the Optional Pegloticase + MTX Extension Period divided by number of doses taken during the Optional Pegloticase + MTX Extension Period)
  - Number of subjects with any dose reduction (reduction in prescribed dose for reason of abnormal labs, AE, or titration down) in the Optional Pegloticase + MTX Extension Period.

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

- Total MTX dosage (in mg) received
- Number of subjects with any dose reduction (reduction in prescribed dose for reason of abnormal labs, AE, or titration down).
- 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 Treatment 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 30 days after the last dose of MTX for subjects who do not receive pegloticase. TEAEs during the Pegloticase + MTX Treatment Period are defined as events that occur after the start of the first pegloticase infusion through 30 days 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 periods 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 for the MTX Run-in Period and Pegloticase + MTX Treatment 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 Treatment period only)
- Serious TEAEs Related to MTX

- Serious TEAEs Related to pegloticase (applicable to Pegloticase + MTX Treatment 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 Treatment 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 Treatment period only)
- TEAEs leading to death

An overall summary of post-treatment AEs, AEs that occur more than 30 days after the last dose of pegloticase and/or MTX, 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 with a Rheumatology CTC grade of 3 or higher
- 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, Pegloticase + MTX Treatment Period, and post-treatment period.
- Subject incidence of TEAEs by MedDRA SOC, PT, and maximum Rheumatology CTC grade, for the MTX Run-in Period and Pegloticase + MTX Treatment 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 Treatment 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 Treatment 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 Treatment 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 Treatment 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 Treatment Period

Each AE summary will be displayed by cohort and overall. Summaries that are displayed by SOC and preferred terms (PT) will be ordered alphabetically by SOC and by PT within SOC. Event incidence rates adjusted by patient year exposure to study drug 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 who continues into the Pegloticase + MTX Treatment Period will be derived as (first dose date of pegloticase in the Pegloticase + MTX Treatment Period – first dose date of MTX)/365.25. The patient-years of exposure for the MTX Run-in Period for each subject who does not continue in the Pegloticase + MTX Treatment Period will be derived as (last dose date of MTX in the MTX Run-in Period – first dose date of MTX + 1)/365.25. The patient-years of exposure for the Pegloticase + MTX Treatment Period for each subject will be derived as (last dose date of MTX or pegloticase (whichever is later)– first dose date of pegloticase + 1)/365.25.

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 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).

If 3 or more events of anaphylaxis occur, events will also be reviewed by an external adjudication committee. Events as reviewed by the external adjudication committee will be summarized separately.

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 IRs including anaphylaxis (investigator reported) will be summarized overall and by severity of event by the following categories for both CCI [redacted]:

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

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) (broad), Torsade de pointes/QT prolongation (broad), Arrhythmia related investigations, signs and symptoms (broad), Cardiomyopathy (broad), Supraventricular tachyarrhythmias (narrow), Ventricular tachyarrhythmias (narrow), Conduction defects (narrow)
- All PTs under SOC of Cardiac disorders
- HLGT Aneurysm

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

Cardiovascular events will be tabulated only if 5 or more subjects have experienced a cardiovascular event. 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.

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 periods (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 central 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 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").

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 (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.

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, diastolic blood pressure, and temperature), weight and BMI 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 Pegloticase + MTX Treatment period, vitals will be measured pre-infusion and post-infusion. Weight will only be measured at Screening, pre-infusion on Day 1, pre-infusion at Week 24, at the non-infusion end of pegloticase infusions visit (if applicable) and at Week 24 or 48/End of Trial/Early Termination Visits.

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. All ECG results will be listed.

15. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

There are no changes to the protocol-specified analyses.

16. REFERENCES

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CCI [redacted].

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.

17. APPENDICES

APPENDIX A: PRESENTATION OF DATA AND PROGRAMMING SPECIFICATIONS

Scoring for the CCI

For each of the [redacted] sections of the CCI [redacted]

The aids and devices are assigned to the individual sections as follows:

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

CCI [redacted]

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.

Gout History

If date of first gout attack or date of first gout diagnosis are incomplete, impute as follows for calculating time since first gout attack and time since first gout diagnosis:

- If day is missing, impute as first day of month.
- If day and month are missing, impute as January 1 of the year.
- If year is missing, do not impute and time since date will be missing.

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

CCI

CCI

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

[redacted]

[redacted]

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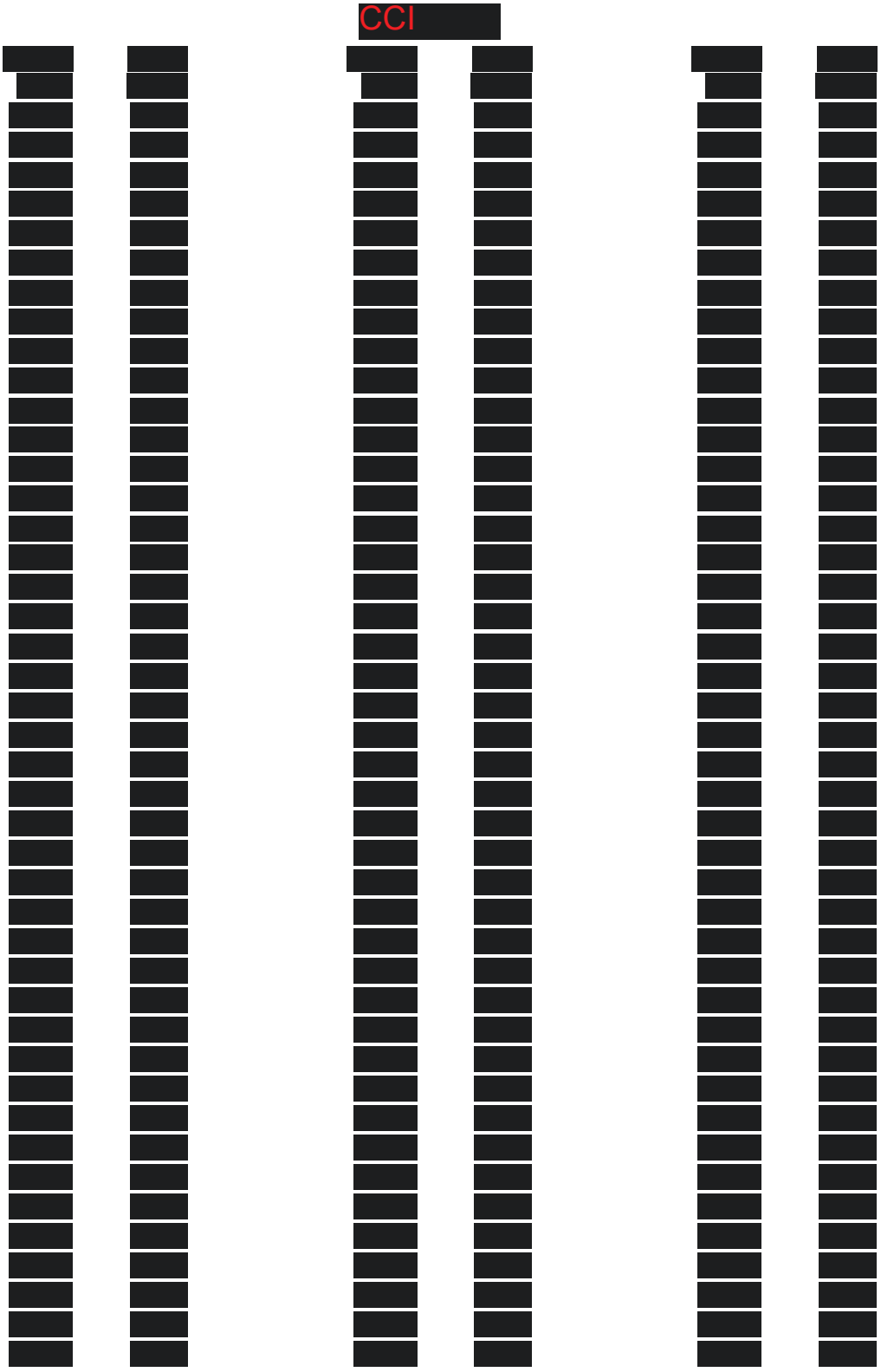
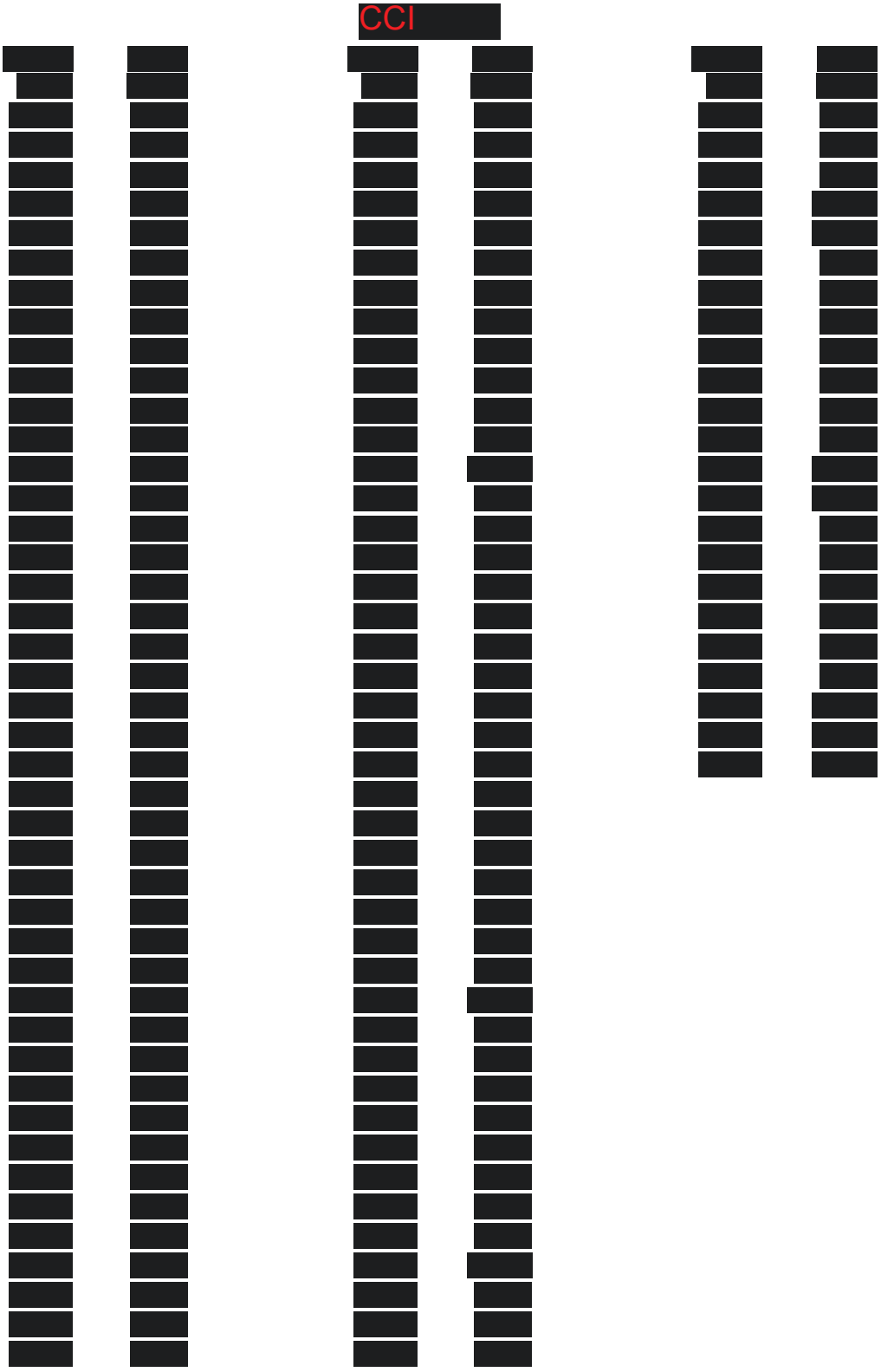
[redacted]

[redacted]


CCI

CCI [redacted] [redacted] [redacted] [redacted] [redacted]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CCI [redacted] [redacted] [redacted]

APPENDIX C: LIST OF TABLES, LISTINGS, AND FIGURES

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	

[redacted]

Table Number	Table Title	Analysis Set
CCI		

Table Number	Table Title	Analysis Set

Table Number	Table Title	Analysis Set
CCI		

Table Number	Table Title	Analysis Set
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Index of Section 16.2

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