Statistical Analysis Plan

Sponsor Name: Horizon Therapeutics Ireland, DAC

Protocol Number: HZNP-KRY-406
Protocol Title: A Multicenter, Open-Label, Efficacy and Safety Study of Pegloticase in Patients With Uncontrolled Gout Who Have Undergone Kidney Transplantation

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1.0	26-Aug-2020	[redacted]	Final Signed Version

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

Approvals

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1. Glossary of Abbreviations

Abbreviation	Description
ADA	Anti-Drug Antibody (ies)
AE	Adverse Event
AESI	Adverse Event of Special Interest
AZA	Azathioprine
BP	Blood Pressure
cDNA	Complementary Deoxyribonucleic Acid
CFR	Code of Federal Regulations
CI	Confidence Interval
C	Creatinine
CR	Complete Response
COVID-19	Coronavirus Disease 2019
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DECT	Dual-Energy Computed Tomography
DI	Disability Index
dL	Deciliter
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration
G6PD	Glucose-6-Phosphate Dehydrogenase
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBV	Hepatitis B Virus
HEENT	Head, Eyes, Ears, Nose, and Throat
Hg	Mercury
HIPPA	Health Insurance Portability and Accountability Act

Abbreviation	Description
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council For Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IND	Investigational New Drug
IR	Infusion Reaction
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous(Ly)
kDa	Kilodalton
L	Liter
µm	Micrometer
µmol	Micromole
MAP	Mean Arterial Pressure
MDRD	Modification Of Diet in Renal Disease (Equation)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intention-To-Treat
mL	Milliliter
mm	Millimeter
mPEG	Methoxy- Poly(Ethylene Glycol)
MR	Marked Response
mRNA	Messenger Ribonucleic Acid
NIAID	National Institute of Allergy and Infectious Diseases
ODA	Orphan Durg Act
PBMC	Peripheral Blood Mononuclear Cell
PBS	Phosphate-Buffered Saline
PD	Progressive Disease
PEG	Poly(Ethylene Glycol)
PI	Principal Investigator

Abbreviation	Description
PK	Pharmacokinetic(S)
PO	Oral
PR	Partial Response
pUA	Plasma Uric Acid
QoL	Quality Of Life
RCT	Randomized Controlled Trial
RCTC	Rheumatology Common Toxicity Criteria
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
Scr	Serum Creatinine
SD	Stable Disease
sUA	Serum Uric Acid
TFG	Treatment Failure Gout
UA	Uric Acid
UACR	Urine Albumin-To-Creatinine Ratio
UE	Unable To Evaluate
ULT	Urate Lowering Therapy
USP	United States Pharmacopeia
VAS	Visual Analog Scale

Note: Abbreviations used only once in a paragraph or in tables or figures are defined within the relevant paragraph, table, or figure.

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures for the HZNP-KRY-406 study which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

[redacted] will develop the statistical analysis plan (SAP) and table, listing and figure (TLF) shells.

2.2. Timings of Analyses

The primary analysis of safety, efficacy and pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study. Additional summary of the data may be performed periodically throughout the study, and safety data will be summarized regularly for safety monitoring by the Sponsor.

2.3. Coronavirus Disease 2019 (COVID-19)

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

3. Study Objectives

3.1. Primary Objective

To evaluate the effect of pegloticase on the response rate of sustained serum uric acid (sUA) reduction to sUA <6 mg/dL during Month 6 of treatment.

3.2. Secondary Objectives

- To evaluate the effect of pegloticase on the response rate of sustained serum uric acid reduction to sUA <5 mg/dL during Month 6 of treatment;
- To evaluate the effect of pegloticase on pain assessed by the Health Assessment Questionnaire (HAQ) pain score; and
- To evaluate the effect of pegloticase on disability assessed by the Health Assessment Questionnaire - Disability Index (HAQ-DI) score.

3.3. Exploratory Objectives

- [redacted]
- To evaluate the pharmacokinetics (PK) of pegloticase and the profile of anti-methoxy-poly(ethylene glycol) (PEG) and anti-uricase IgG antibodies; and
- To evaluate the safety and efficacy 3 months after the end of treatment with pegloticase.

3.4. Safety and Tolerability Objectives

To assess the overall adverse event (AE)/serious AE (SAE) profile including AEs of special interest (AESI) (infusion reactions [IRs], anaphylaxis, gout flares and cardiovascular [CV] events), laboratory tests, vital signs and physical exam, and incidence of biopsy confirmed renal rejection.

4. Study Design

4.1. Brief Description

This study is a Phase 4, multicenter, open-label, efficacy and safety study of pegloticase with uncontrolled gout who have undergone kidney transplantation. Twenty subjects are planned to be enrolled.

The study design will include: 1) a Screening Period, lasting up to 35 days; 2) a 24-week treatment period which includes an End-of-Study (Week 24)/Early Termination Visit; 3) a safety follow-up phone/email Visit 30 days after the last infusion; and 4) a 3-month post-treatment follow up visit.

Samples for measurement of sUA levels will be collected at the Screening Visit, prior to each infusion, 15-60 minutes after the end of each infusion and at the End-of-Study/Early Termination Visit. Additional samples for sUA levels will be collected at non-infusion Visits at Weeks 21 and 23.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria during Screening will be enrolled at the Day 1 Visit to receive pegloticase 8 mg administered IV every 2 weeks from Day 1 through Week 22, inclusive. During this 24-week treatment phase, subjects who meet the individual subject sUA stopping rule (pre-dose sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit) or discontinue treatment for any other reason will complete the End-of-Pegloticase-Infusions Visit procedures within 2 weeks and be encouraged to continue to participate in all visits through the end of the study. Subjects will return for regularly scheduled visits and will complete all study visit procedures with the exception of the pegloticase infusion and IR prophylaxis. After the Week 24 Visit (or End-of-Pegloticase-Infusions Visit [if applicable]), subjects should resume regular care for gout per the judgment of the treating physician, including resumption of urate-lowering therapy (ULT) upon pegloticase discontinuation, if appropriate. Subjects will have a 3-Month Follow-up visit to assess clinical status, including sUA levels.

On days of scheduled infusions, pegloticase will be administered after all pre-dose visit assessments have been completed. The date and start and stop time of infusion will be recorded. The date of the first dose of pegloticase is defined as Day 1. All subsequent doses and study visits will be scheduled based on the Day 1 visit date.

It is required that before a subject begins the treatment period, he or she has been taking protocol defined standard gout flare prophylaxis (colchicine at initial dose of 0.3 to 0.6 mg/day if tolerated and low-dose prednisone ≤ 10 mg/day; for subjects already taking chronic corticosteroids, only colchicine 0.3 to 0.6 mg/day should be added). In subjects with eGFR ≤ 30 mL/min/1.73m^2, the dose of colchicine should not be more than 0.3 mg/day. In subjects taking cyclosporine, only low dose prednisone (and not colchicine) should be used for ≥ 1 week before the first infusion. Gout flare prophylaxis should continue for the duration of the 24-week treatment period. Subjects should be monitored closely for symptoms of colchicine excess during the study. Reductions in dose, dose frequency or discontinuation of colchicine are permitted if not tolerated.

For Infusion Reaction (IR) prophylaxis, fexofenadine (60 or 180 mg orally) will be taken the day before each infusion; fexofenadine (60 or 180 mg orally) and acetaminophen (1000 mg orally) will be taken in the morning before each infusion; and methylprednisolone (125 mg IV from Day 1 to Week 10 and 80 mg IV from Week 12 until the end of treatment) will be administered over a methylprednisolone infusion duration between 10 and 30 minutes, immediately prior to each pegloticase infusion. Alternate IV corticosteroid regimen may be substituted for methylprednisolone at the discretion of the Investigator. The dose of fexofenadine should be 60 mg orally in subjects with decreased renal function and 180 mg orally in subjects with normal renal function (eGFR >90 mL/min/1.73m^2).

Serum samples for PK analysis of pegloticase will be collected approximately 15 minutes to 2 hours after the end of infusion on Day 1, prior to the infusion and approximately 15 minutes to 2 hours after the end of infusion at Weeks 2, 6, 14 and 22. An additional PK sample will be collected at the Week 21 non-infusion visit, End-of-Pegloticase-Infusions Visit (if applicable) and End-of-Study/Early Termination Visit.

Serum samples for evaluation of anti-PEG and anti-uricase immunoglobulin G (IgG) antibodies will be collected prior to the infusion on Day 1 and prior to the infusions at the Weeks 2, 6, 14 and 22. An additional sample will be collected at the End-of-Pegloticase-Infusions Visit (if applicable), End-of-Study/Early Termination Visit and the 3-month follow up visit. In the event of an AE suspected to be an infusion reaction, a sample will be collected at that time or at the subsequent visit for future evaluation of antibodies.

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

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

4.2. Determination of Sample Size

A sample size of 20 subjects is planned for this study. The primary efficacy endpoint, the proportion of subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6, will be demonstrated to be statistically greater than 43.5% (proportion of responders during Month 6 in the Phase 3 studies), if at least 14/20 (70%) responders are observed. In that case, the lower bound of a 95% confidence interval for the proportion of responders will be about 46%.

The COVID-19 pandemic outbreak occurred midway through enrollment for the study, which has affected some subject enrolment and data acquisition during the trial. As a result, the sponsor may enroll approximately 1- 2 additional subjects (for a total of 21-22 treated subjects) in order to obtain information equivalent to study at least 20 subjects not impacted by COVID-19.

4.3. Treatment Assignment & Blinding

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

[redacted] will be used to assign subjects specific pegloticase kit numbers.

Specific procedures for accessing and assigning study drug through [redacted] are contained in the study procedures manual.

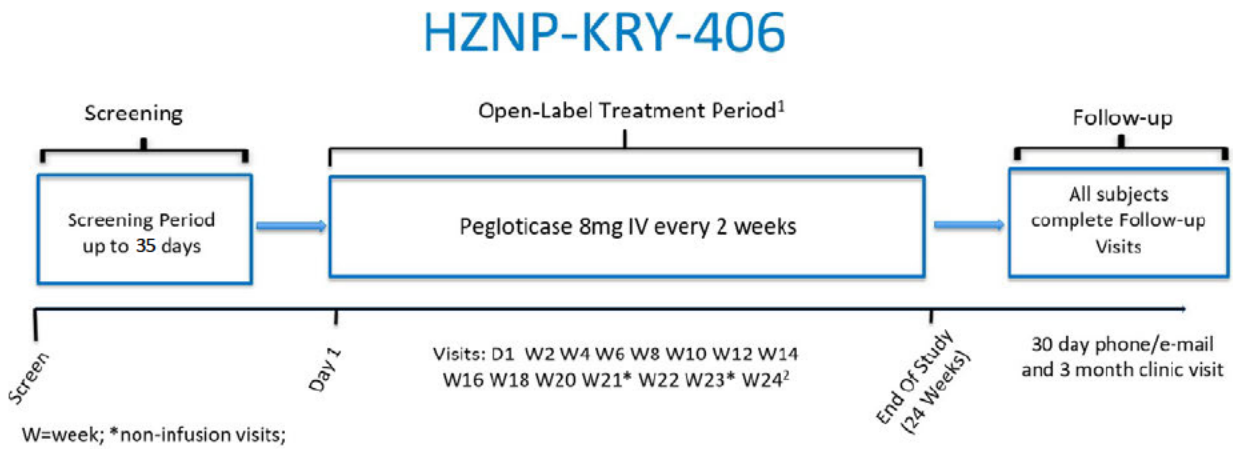
4.4. Administration of Study Medication

Starting at the Day 1 visit, subjects will receive pegloticase at a dose of 8 mg administered IV every 2 weeks for a total of 12 infusions from Day 1 through the Week 22 Visit.

After the Week 24 Visit, subjects should resume regular care for gout per the judgment of the treating physician, including resumption of ULT upon pegloticase discontinuation, if appropriate. Subjects will have a 3-month Follow-up visit to assess clinical status, including sUA levels.

4.5. Study Procedures and Flowchart

The flowchart copied from the protocol, Section 9.1, is reproduced here. The number of days in the screening period has been updated from 28 days to 35 days to correspond to the change to screening period length made in protocol amendment 1.0.



W=week; *non-infusion visits;

1. Subjects will receive pegloticase 8 mg administered IV every 2 weeks from Day 1 through Week 22, inclusive. During this 24-week treatment phase, subjects who meet the sUA based stopping rule or discontinue treatment for any other reason will complete the End-of-Pegloticase-Infusions Visit and will continue in the study until the Week 24/End-of-Study/Early Termination Visit. After the End-of-Pegloticase-Infusions Visit, subjects will return for regularly scheduled visits and will complete all study visit procedures with the exception of the pegloticase infusion and IR prophylaxis.
2. The Week 24 Visit is the End-of-Study Visit for pegloticase responders and those that met the stopping rule or discontinued treatment, but continued in the study until Week 24. The Early Termination Visit is for all other subjects that withdrew from the study prior to Week 24.

The schedule of assessments is copied from the protocol.

Study Procedure/ Assessment	Screening	Treatment Period[2] Day 1 through Week 24													End of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-Study/ Early Termi-nation	Safety Follow-up Phone/ Email Visit	Post-Treatment Follow-Up[4]
			Week (±3 d)												Within 2 weeks		30 days	
	Screening Visit[1]	Day 1	2	4	6	8	10	12	14	16	18	20	21	22	23	following final infusion if prior to Wk 22	Wk 24 (±3 d)	after last pegloticase infusion (±3 d)	3 months
Informed consent	X																		
Demographic data	X																		
Inclusion/exclusion criteria	X	X																	
Medical/surgical history[5]	X																		
Medication/ substance use history[6]	X																		
Physical examination[7]	X	X		X		X		X		X		X				X	X		X
Vital signs, height, and weight[8]	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X		X
[redacted]		[redacted]			[redacted]			[redacted]			[redacted]					[redacted]	[redacted]		
Electrocardiogram[9]	X																		
AE/SAE Assessment[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
HAQ-DI, HAQ Pain Scale [redacted]	X	X			X				X			X				X	X		X

Study Procedure/ Assessment	Screening	Treatment Period[2] Day 1 through Week 24													End of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-Study/ Early Termi-nation	Safety Follow-up Phone/ Email Visit	Post-Treatment Follow-Up[4]
			Week (±3 d)												Within 2 weeks		30 days	
	Screening Visit[1]	Day 1	2	4	6	8	10	12	14	16	18	20	21	22	23	following final infusion if prior to Wk 22	Wk 24 (±3 d)	after last pegloticase infusion (±3 d)	3 months
[redacted]	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮	▮		▮
[redacted]	▮	▮			▮				▮			▮				▮	▮		▮
[redacted]	▮								▮							▮	▮		
[redacted]	▮	▮							▮							▮	▮		▮
Gout prophylaxis Rxs filled[13]		Rxs filled as needed																	
Fexofenadine Rx filled[14]		Rxs filled as needed																	
Infusion reaction prophylaxis[15]		X	X	X	X	X	X	X	X	X	X	X		X					
IR prophylaxis compliance (Yes/No)		X	X	X	X	X	X	X	X	X	X	X		X					
Gout flare prophylaxis compliance (Yes/No)		X	X	X	X	X	X	X	X	X	X	X		X		X			
Pegloticase infusion		X	X	X	X	X	X	X	X	X	X	X		X					
Pegloticase PK sampling[16]		X	X		X				X				X	X		X	X		
sUA[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Study Procedure/ Assessment	Screening	Treatment Period[2] Day 1 through Week 24													End of-Pegloticase-Infusions Visit[3] (if applicable)	End-of-Study/ Early Termi-nation	Safety Follow-up Phone/ Email Visit	Post-Treatment Follow-Up[4]
			Week (±3 d)												Within 2 weeks following final infusion if prior to Wk 22	Wk 24 (±3 d)	30 days after last pegloticase infusion (±3 d)	3 months
	Screening Visit[1]	Day 1	2	4	6	8	10	12	14	16	18	20	21	22	23				
Blood UA by POC (if devices are provided) [17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology	X	X	X		X				X					X		X	X		X
Clinical chemistry	X	X	X		X				X					X		X	X		X
Blood and Urine Collection for Allantoin[22]		X	X	X	X	X	X		X		X			X		X	X		X
Spot urine collection for UACR	X	X	X		X				X					X		X	X		X
Samples for Antibody testing[18]		X	X		X				X					X		X	X		X
HBV Serology	X																		
Sample for G6PD	X																		
Pregnancy test[19]	X	X		X		X		X		X		X				X	X		
Blood Biomarker sampling[20]	X			X					X							X	X		
Principal Investigator assessment of subject clinical status and treatment goals[21]	X															X	X		

Abbreviations: AE = adverse event; d = day(s); DECT = dual-energy computed tomography; G6PD = glucose-6-phosphate dehydrogenase; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBV = hepatitis B virus; IR = infusion reaction; PK = pharmacokinetic; Rx = prescription; SAE = serious adverse event; sUA = serum uric acid; UACR= Urinary Albumin Creatinine Ratio; V = Visit; wk(s) = week(s)

Footnotes:

1. The Screening Visit can occur up to 35 days prior to the Day 1 Visit.
2. Subjects will be enrolled at the Day 1 Visit to receive pegloticase 8 mg administered IV every 2 weeks from Day 1 through Week 22, inclusive. During this 24-week treatment phase, subjects who meet the sUA based stopping rule or discontinue treatment for any other reason will complete the End-of-Pegloticase-Infusions Visit procedures within 2 weeks and be encouraged to continue to participate in all visits through the end of the study. Subjects will return for regularly scheduled visits and will complete all study visit procedures with the exception of the pegloticase infusion and IR prophylaxis. After the Week 24 Visit (or End-of-Pegloticase-Infusions Visit [if applicable]), subjects should resume regular care for gout per the judgment of the treating physician, including resumption of urate-lowering therapy (ULT) upon pegloticase discontinuation, if appropriate. Subjects will have a 3-month Follow-up visit to assess clinical status, including sUA levels.
3. Subjects who end treatment due to the stopping rules or other reasons should complete the End-of-Pegloticase-Infusions Visit within 2 weeks of the last infusion. Subjects should remain on study. See Protocol Section 9.3.3.1.1for details on visits and procedures.
4. All subjects will have a follow up visit 3 months following the End-of-Pegloticase Infusions Visit or Week 24/End-of-Study/Early Termination Visit. If the subject ends treatment early but remains in the study and the 3-month Post Treatment Follow-up Visit occurs prior to Week 24, the 3-month Post Treatment Follow-up Visit will be adjusted accordingly based on the timing of the last treatment.
5. The Investigator or designee will collect a complete gout history and other relevant medical/surgical history.
6. Medication history (i.e., prior medications) will include gout medications, starting at the time of diagnosis and up to (but not including) the Day 1 Visit; substance use history; and all other medications up to (but not including) the Day 1 Visit. Prior concomitant medications (not including gout medications) will be collected for 1 year prior to Screening.
7. A complete physical examination will be performed at the Screening Visit and will include assessments of head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, extremities, neurological status and musculoskeletal system, and for presence of tophi, as well as gout history and symptom severity. A targeted physical examination (for joint and skin evaluation and assessment of AEs) will be conducted based on potential risk for or occurrence of AEs at Day 1, and prior to administration of infusion at Weeks 4, 8, 12, 16, and 20, the End-of-Pegloticase-Infusions Visit (if applicable), Week 24/End-of-Study/Early Termination Visit and 3-month Post-Treatment Follow Up Visit; at a minimum this should include heart, lungs, and abdomen. Clinically significant findings from the targeted physical examinations will be recorded as AEs.

8. BP, respiratory rate, temperature, and heart rate will be measured at every visit, BEFORE study drug infusion and any scheduled blood draws. Heart rate and BP measurements should be taken after the subject has been in a sitting position and in a rested and calm state with proper positioning including back support, feet flat on the floor, for at least 5 minutes (See Section 9.5.4.4 for detailed BP measurement procedures). Subject's arm should be supported at heart level; and the cuff placed on the bare arm. A large cuff should be used as needed to fit the upper arm and the same arm is to be used consistently at each study visit. The Korotkoff phase V will be used to determine DBP. The cuff deflation rate should be 2 mmHg per second. [redacted] MAP will be calculated from SBP and DBP as MAP = 1/3 * SBP + 2/3 * DBP. Weight should be measured in kilograms or pounds without shoes and recorded at the Screening Visit, prior to pegloticase infusion on Day 1, at the Week 8 and 16 Visits, the non-infusion End of Pegloticase Infusions Visit (if applicable), the Week 24/End of Study/Early Termination Visit, and the 3 month Post Treatment Follow-up Visit. Height will be collected at the Screening Visit only.
9. Electrocardiogram should be completed during Screening. The electrocardiogram is read at the site. If a subject experiences an AE suspected to be an IR, a 12-lead ECG will also be performed.
10. AEs/SAEs will be collected from the time of signature of the ICF until the 3-month Post-Treatment Follow-up Visit. For each AE, the Investigator will be asked to record if the event was possibly an infusion reaction or anaphylaxis and if so, will be prompted to complete additional eCRFs.
11. [redacted]
13. Subjects are required to take at least one protocol standard gout flare prophylaxis (i.e., colchicine initial dose 0.3-0.6 mg/day and low-dose prednisone ≤ 10 mg/day); for subjects already taking low dose corticosteroids, colchicine 0.3-0.6 mg/day should be added. In subjects with eGFR ≤ 30 mL/min/1.73m^2, the dose of colchicine should not be more than 0.3 mg/day. In subjects taking cyclosporine, only low dose prednisone (and no colchicine) should be used for ≥ 1 week before the first infusion. Gout flare prophylaxis should continue for the duration of the 24-week treatment period. Subjects should be monitored closely for symptoms of colchicine excess during the study. Reductions in dose, dose frequency or discontinuation of colchicine are permitted if not tolerated.
14. For IR prophylaxis, fexofenadine (60 - 180 mg orally) will be taken the night before each infusion.

15. IR prophylaxis includes fexofenadine administered the day before each infusion; fexofenadine and acetaminophen (1000 mg orally) administered on the morning of each infusion. In addition, methylprednisolone (125 mg IV from Day 1 to Week 10 and 80 mg IV from Week 12 until the end of treatment) is recommended to be administered over an infusion duration between 10 and 30 minutes, immediately prior to each pegloticase infusion. Alternate IV corticosteroid regimen may be substituted for methylprednisolone at the discretion of the Investigator. The dose of fexofenadine should be 60 mg orally in subjects with decreased renal function and 180 mg orally in subjects with normal renal function (eGFR >90 mL/min/1.73m2).
16. For all subjects, serum samples for pegloticase PK analysis will be collected approximately 15 minutes to 2 hours after the end of infusion on Day 1; prior to infusion and approximately 15 minutes to 2 hours after the end of the infusion at Weeks 2, 6, 14, and 22. An additional PK sample will be collected at Week 21, the End-of-Pegloticase-Infusions Visit (if applicable) and the Week 24/End-of-Study/Early Termination Visit.
17. Serum samples for measurement of sUA levels will be collected at the Screening Visit, within 48 hours prior to and after the end of each pegloticase infusion prior to discharge from the site. Additional serum samples for sUA levels will be collected at non-infusion Visits at Weeks 21 and 23 and the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit, and the 3-month Follow-up Visit. For subjects whose previous visit's pre-infusion sUA value is > 6 mg/dL, two separate samples/tubes of blood should be collected within 48 hours prior to the pegloticase infusion (except on Day 1 when only 1 pre-infusion sample is required for the central laboratory); one sample/tube will be assessed by the site's local laboratory for pre-infusion sUA results for on-study subject management. If a local laboratory sample is drawn (within 48 hours prior to the pegloticase infusion), a sample for the central laboratory will be drawn prior to the pegloticase infusion on the day of the visit. The second sample/tube will be sent to the central laboratory for analysis and recording in the database. POC devices may be provided to measure subject uric acid levels in real time. If POC devices are provided, blood uric acid levels prior to each pegloticase infusion and after the end of each pegloticase infusion prior to discharge from the site at the selected visits will recorded in database, but NOT to be used to manage pegloticase treatment. See the Laboratory Manual for instructions for alternate scenarios.
18. Serum samples for evaluation of anti-PEG antibodies and anti-uricase IgG antibodies will be collected prior to the infusion on Day 1 and at Weeks 2, 6, 14, and 22. An additional sample will be collected at each of the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit, and the 3-month Study Follow Up Visit. In the event of an AE suspected to be an infusion reaction, a serum sample will be collected in a serum separating tube at that time or at the subsequent visit for future evaluation of pegloticase antibodies.
19. For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit and at the Week 24/End-of-Study/Early Termination Visit. A urine pregnancy test will be performed at all other indicated visits.
20. Blood samples will be collected from consenting subjects for serum and for peripheral blood mononuclear cell (PBMC) isolation for potential analysis of inflammatory biomarkers, markers related transplant outcome, gout or gout co-morbidities in response to pegloticase or other potential treatment for gout. Subjects who consent to the optional blood draw for analysis of biomarkers but screen fail will be requested to return 24 weeks +/- 4 weeks for an additional blood sample. Adverse events, concomitant medications and vital signs will also be collected as an unscheduled visit at that time.
21. The Investigator will review the clinical status and individual subject treatment goals at Screening, the End-of-Pegloticase-Infusions Visit (if applicable) and the Week 24/End-of-Study/Early Termination Visit.

22. Blood and urine samples will be collected prior to pegloticase infusion on Day 1 and at the Week 2, 4, 6, 8, 10, 14, 18, and 22 Visits, the End of Pegloticase Infusions Visit (if applicable), the Week 24/End of Study/Early Termination Visit, and the 3 month Post Treatment Follow-up Visit. In addition, blood and urine samples will be collected after the end of pegloticase infusions prior to discharge from the site at on Day 1, Week 2, 6, 14 and 22 Visits.

5. Endpoints

5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of Month 6 (Weeks 20, 21, 22, 23 and 24) responders, defined as subjects achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.

5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The proportion of 5 mg/dL responders during Month 6 (Weeks 20, 21, 22, 23 and 24), defined as subjects achieving and maintaining sUA < 5 mg/dL for at least 80% of the time during Month 6;
- The change from baseline in mean HAQ pain score to Week 24; and
- The change from baseline in mean HAQ-DI score to Week 24.

5.3. [redacted]

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

5.4. Pharmacokinetic and Anti-drug Antibody Endpoints

The PK and anti-drug antibody endpoints are:

- Serum concentrations of pegloticase;
- Profile of anti-PEG and anti-uricase IgG antibodies.

5.5. Safety and Tolerability Endpoints

Safety and tolerability endpoints are:

- Overall AE/SAE profile;
    - Incidences of AESI: IRs, anaphylaxis, gout flares, cardiovascular events;
- Laboratory tests: change from baseline to each scheduled assessment;
- Electrocardiogram (ECG)
- Vital signs: change from baseline to each scheduled assessment and physical examination; and
- Incidence of renal rejection (biopsy proven).

6. Analysis Sets

The following analysis populations will be defined for this study:

6.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all subjects who receive at least 1 dose of pegloticase.

The ITT population will be used for analysis of ADA, efficacy and safety data.

6.2. Safety Population

The safety population will include all subjects who receive at least 1 dose of pegloticase; therefore it will be equivalent to the ITT population.

6.3. Pharmacokinetic Population

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

7. Protocol Deviations

All protocol deviations and the reasons for such deviations are documented in the eCRF. Sites will be issued specific instructions to follow in order to capture missed visits, out of window visits, treatment interruptions and treatment discontinuations due to COVID-19 on the eCRF. Details to be recorded include whether a subject has suspected or confirmed COVID-19 infection and whether the study site is open or closed. Deviations will be categorized by type and as major or minor. In the event of a major protocol deviation, the Investigator and Sponsor's Medical Monitor will determine whether the subject should continue to participate in the study.

Total count of protocol deviations will be provided. Major protocol deviations will be summarized by period of occurrence for all subjects in total and by type.

All protocol deviations will be listed, including period of occurrence (screening, treatment period, & follow-up period).

8. General Aspects for Statistical Analysis

8.1. General Methods

- In general, descriptive summaries will be provided. Efficacy summaries will show columns with "Pegloticase" as the treatment group for the ITT population. Safety summaries will be presented similarly.

- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.

- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.

- The same number of decimal places as the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.

- Unless otherwise specified, confidence intervals (CI) will be based on 95% confidence and two-sided.

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

8.2. Key Definitions

8.2.1. Baseline

Unless otherwise specified, baseline is defined as the last non-missing observation prior to the first dose of pegloticase.

For observations occurring on the same date as the first dose of pegloticase (Day 1), time should be considered in the determination of baseline.

For observations occurring on the same date as the first dose of pegloticase (Day 1) where time is not collected but the protocol specifies the evaluation must occur prior to infusion (principle investigator assessment of gout flare, subject self-reported gout flare assessment, HAQ, physician global assessment), the non-missing Day 1 result will be considered the last non-missing observation prior to first dose of pegloticase.

8.2.2. Study Day

Study day will be determined relative to the first infusion of pegloticase. For calculations, for study days on or after the first dose date, the study day will be calculated as assessment date – first dose date + 1. For study days prior to the first dose date, study day will be calculated as assessment date – first dose date. There will be no study day 0.

8.2.3. Age

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

8.3. Missing Data

8.3.1. Medication Dates

8.3.1.1. *Unknown Medication Dates*

There is no imputation for completely missing dates.

8.3.1.2. *Partial Medication Dates*

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

For partial start dates:

- If the month and year are provided and the day is missing, and the month and year match the month and year of the first pegloticase dose date, the first dose date of pegloticase 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, the first dose date of pegloticase will be imputed. Otherwise, January 1st will be used.
- 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.

8.3.2. Adverse Events Information

8.3.2.1. *Dates*

For adverse events with incomplete dates or times, 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 Pegloticase Treatment 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 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 Treatment 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.

- 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 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 Treatment Period.
    - Otherwise, January 1st will be used and the treatment-emergent status will be assessed relative to the dosing start date of pegloticase.
- If the start date is completely missing, the AE will be considered treatment-emergent in the Pegloticase Treatment 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 an adverse event occurs on the same day as the first dose date of pegloticase but time is missing, then the AE will be considered treatment-emergent in the Pegloticase Treatment Period.

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.

8.3.2.2. *Relationship and Severity*

Events with missing relationship to study drug in the Pegloticase Treatment Period will be considered "related" to pegloticase for statistical summaries.

Events with missing severities will be considered "severe" or Rheumatology CTC Criteria "Grade 3" for statistical summaries.

8.3.3. Missing Data due to COVID-19

No imputation of missing data will be done for subjects who miss assessments or postpone assessments due to COVID-19. Only the observed data will be used in data summaries, when indicated.

Additional details of how the missing data will be handled in analysis are provided in sections 10.2, 10.3 and 10.4 for each endpoint.

8.4. Visit Windows

For all analyses, data will be summarized according to the scheduled visit and time points as outlined in the protocol and by the visit denoted on the electronic case report form (eCRF). Further, the End of Study/Early Termination (ET) and End of Pegloticase visit will be windowed to a visit based on the study day of occurrence relative to the target day of each scheduled visit according to Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6 below.

Table 1 shows windows for the gout flares assessments and sUA collections. Table 2 shows windows for the vital signs. Table 3 shows windows for the laboratory assessments and anti-drug-antibodies. Table 4 shows windows for the HAQ-DI, HAQ Pain Scale [redacted]
Table 5 shows windows for the PK assessments. Table 6 shows windows for the blood and urine collection for allantoin.

Unscheduled sUA visits, assessed by the central laboratory or local laboratory (see Section 10.1), will be assigned an analysis window according to the tables below. These unscheduled visits will be used for the determination of sUA responder, but will not be included in table summaries.

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

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

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

Table 2: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (Vital Signs)

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

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

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

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

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

Table 4: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (HAQ-DI, HAQ Pain Scale [redacted]

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase Treatment	Day 1	1	1
	Week 6	43	2 – 71
	Week 14	99	72 – 120
	Week 20	141	121 – 155
	Week 24	169	≥156

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

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

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase Treatment	Day 1	1	1
	Week 2	15	2 – 29
	Week 6	43	30 – 71
	Week 14	99	72 – 124
	Week 21	148	125 – 152
	Week 22	155	153 – 162
	Week 24	169	≥163

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

Table 6: Visit Windows for Assigning End of Study/ET and End of Pegloticase Visits to a Scheduled Visit (Blood and Urine Collection for Allantoin)

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
Pegloticase Treatment	Day 1	1	1
	Week 2	15	2 – 22
	Week 4	29	23 – 36
	Week 6	43	37 – 50
	Week 8	57	51 – 64

Study Period	Visit	Target Day [a]	Window for Reassignment to Scheduled Visit (days)
	Week 10	71	65 – 85
	Week 14	99	86 – 113
	Week 18	127	114 – 141
	Week 22	155	142 – 162
	Week 24	169	≥163

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

In the event that an End of Study/ET or End of Pegloticase visit is reassigned to a visit for which the subject has scheduled data collected, the data from the nominal scheduled visit will take precedence and the data from the End of Study/ET or End of Pegloticase visit will not be summarized. If the End of Study/ET or End of Pegloticase visit maps to a visit where the assessment was scheduled to be collected, and a scheduled collection is not available at that time point, the End of Study/ET or End of Pegloticase visit data will be summarized in the scheduled visit assessment.

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

8.5. Pooling of Centres

Data from all sites will be summarized together for analyses.

8.6. Subgroups

No subgroup analyses are planned for the study.

9. Subject Disposition, Demographic, Other Baseline Characteristics and Medication

9.1. Subject Disposition and Withdrawals

A summary of subject disposition will be provided including the number of subjects screened (All Subjects) and number and percentage of screen failures, as well as the number of subjects in each analysis population (ITT and PK Populations), the number and percentage of subjects who complete the study, who have 30 days and 3 months of follow-up, who complete therapy, who discontinue therapy before the Week 22 infusion, and who discontinue the study prematurely along with the reasons for discontinuation of therapy and study, respectively, will be summarized. The number and percentage of subjects with discontinuation of treatment or study due to COVID-19 will be summarized as part of the reasons for discontinuation.

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

9.2. Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented overall for the ITT Population and PK Population.

The characteristics being summarized include: age, age category (< 65 years, ≥ 65 years), sex, race, ethnicity, time since first gout attack [in years], time since first diagnosis of gout (in years), presence of uric acid crystals confirming diagnosis, number of acute gout flares in the past 12 months, number of acute gout flares in the past 6 months, number of acute gout flares in the past month, pattern of flares, typical severity of acute flares, chronic gout synovitis/arthropathy, prior occurrence of tophi, occurrences of overnight stays in the hospital due to gout, occurrence of surgery for gout [excluding arthrocentesis], prior occurrence of kidney stones, number of episodes of renal colic in the past year [for subjects answering 'Yes' to having kidney stones], kidney function affected by gout, origin of kidney, time since kidney transplant (years), has subject experienced acute rejection in the last 1 year, urate lowering therapy history, tobacco use history, current tobacco use status, alcohol use, other substance use, weight, height, body mass index (BMI), body surface area (BSA), baseline estimated glomerular filtration rate (eGFR) calculated by MDRD, and baseline urine albumin creatinine ratio (UACR).

Age, time since first gout attack, time since first diagnosis of gout, number of acute gout flares in the past 6 months, number of acute gout flares in the past month, number of episodes of renal colic in the past year, time since kidney transplant (years), weight, height, BMI, and BSA will be summarized as continuous variables showing number of non-missing values, mean, standard deviation, median, minimum and maximum.

Age category, sex, race, presence of uric acid crystals confirming diagnosis, number of acute gout flares in the past 12 months (1 flare, 2-3 flares, 4-9 flares, and 10 or more flares), number of acute gout flares in the past 6 months (1 flare, 2 flares, 3-5 flares, and > 5 flares), number of acute gout flares in the past month (1 flare, 2 flares, 3-5 flares, and > 5 flares), pattern of flares (1 joint, 2-3 joints, >3 joints), typical severity of acute gout flares (mild, moderate, severe), chronic gout synovitis/arthropathy, prior occurrence of tophi, occurrences of overnight stays in the hospital due to gout, prior occurrence of surgery for gout [excluding arthrocentesis], prior occurrence of kidney stones, number of episodes of renal colic in the past year (0 episodes, 1 – 2 episodes, 3 or more episodes), kidney function affected by gout, origin of kidney, has subject experienced acute rejection in the last 1 year, urate lowering therapy history, tobacco use history,

current tobacco use status, alcohol use, and other substance use will be summarized using categorical values.

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

Time (years) 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.

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

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

The following formulas are used:

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight(kg)/[Height(m)^2]

BSA (m^2) = √ [((height in cm) x (weight in kg)) / 3600] (Mosteller Formula)

9.3. Medical History and Concomitant Diseases

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

Medical history data will also be listed.

9.4. Medication

9.4.1. Determination of Period of Use

- Prior Medication:
    - Any medication with a start date prior to the date of first dose of pegloticase will be considered a prior medication.
- Concomitant in the Pegloticase Treatment Period:
    - Any medication indicated as “Ongoing at end of study” or with a stop date on or after the first infusion date of pegloticase but excluding medications with start date more than 30 days after the date of the end of the last pegloticase infusion.
- Follow-up Medication:

- Any medication with 1) a start date prior to 30 days after last dose of study medication that continued use or had a stop date on or after 30 days after the last dose of study medication, or 2) a medication with a start date more than 30 days after the last dose of study medication.

For medications with missing dates, the following rules will be used to assign prior, concomitant, and follow-up (concomitant medications used > 30 days of the last dose of pegloticase) status to a medication:

Medication Start Date	Medication End Date	Prior	Concomitant in Pegloticase Treatment Period	Follow-up (> 30 days of either End of Pegloticase or Week 24 Visits)
Unknown	Unknown	Yes	Yes	Yes
Unknown	< first dose of pegloticase	Yes	No	No
Unknown	≥ first dose of pegloticase and ≤ 30 days after last dose of pegloticase	Yes	Yes	No
Unknown	> 30 days after last dose of pegloticase	Yes	Yes	Yes
< first dose of pegloticase	Unknown	Yes	Yes	Yes
≥ first dose of pegloticase and ≤ 30 days after last dose of pegloticase	Unknown	No	Yes	Yes
> 30 days after last dose of pegloticase	Unknown	No	No	Yes

Details on handling of missing and incomplete dates are provided in Section 8.3.1.

9.4.2. Presentation of Data

Medications will be coded using World Health Organization (WHO) Drug Global B3 September 2018 dictionary.

Prior, concomitant medications used during the Pegloticase Treatment Period, and follow-up (concomitant medications used > 30 days of last dose of pegloticase), will each be summarized by presenting the counts and percentage of subjects using medications overall for the ITT Population.

Separate summary tables will present concomitant and follow-up immunosuppresants (ATC2 = "IMMUNOSUPPRESANTS"). Gout medications (ATC2 = "ANTIGOUT PREPARATIONS") taken post-treatment (start date after the last pegloticase infusion) will be summarized as well.

Summaries will be presented by Anatomical Therapeutic Chemical (ATC) Level 4 term and preferred drug name. Medication summaries will be sorted alphabetically by Anatomical Therapy Chemical (ATC) Level 4 and by preferred drug name within ATC Level 4. Subjects will be counted only once for each medication class and each preferred drug name.

Prior, concomitant medications used during the Pegloticase Treatment Period, and follow-up medications, will be listed together with a designation to identify the period(s) of usage and sorted by start date.

Period of usage is determined based on the criteria presented in section 9.4.1.

9.5. Concomitant Procedures

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

10. Efficacy

All efficacy analyses will be performed on the ITT population, unless otherwise specified.

10.1. Handling Rules for sUA Values

Serum samples for measurement of sUA levels are scheduled for collection at the Screening Visit (Within 35 Days of the Day 1 Visit), and prior to and after the end of each pegloticase infusion before discharge from the Pegloticase Treatment Period. Additional serum samples for sUA levels are collected at non-infusion Visits at Weeks 21 and 23 and the End of Pegloticase Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit, and the 3-month Follow-up Visit. Subjects with a pre-infusion sUA level >6 mg/dL at 2 consecutive study visits beginning with the Week 2 Visit will discontinue pegloticase and complete the End of Pegloticase Infusions Visit (if applicable) or the Week 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 at a visit only when the central laboratory-processed value at a time point is not available, but the local lab-processed pre-infusion value, collected value at the same time point, is available.

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

10.2. 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 (if available), and post-infusion samples with non-missing sUA values.

The Month 6 period will include pre-infusion and post-infusion results at Week 20, results at Week 21, pre-infusion and post-infusion results at Week 22, results at Week 23, and results at Week 24 processed by the central laboratory. 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. Section 10.1 shows the rules for inclusion of sUA values reported by local laboratories.

There will be no imputation of sUA values due to missed collections among those collected between Week 20 and Week 24. Only observed values will be included in the calculation. If central lab results are available, central lab results are used. If central lab results aren't available, local lab results will be used.

[redacted]

Results from visits where an infusion was not performed (e.g. subject discontinued pegloticase but remained in study) will be used when available. The only exception to this approach is for subjects meeting the stopping rule. Subjects meeting the stopping rule prior to Week 24 will be counted as non-responders. 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.

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) 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.

Sensitivity Analysis for the Primary Endpoint

The primary efficacy analysis will be repeated for the ITT Population to (1) include all sUA results (if available) in the response calculation following discontinuation of treatment for subjects who meet stopping rule and continue in the study (2) include all sUA results corresponding to the Month 6 primary analysis period (if available) in the response calculation following any COVID-19-related missing sUA assessments or disruption in treatment (excluding the first pre-infusion sUA after return from COVID-19-related pause in treatment).

[redacted] Secondary Efficacy Endpoints and Analyses

Observed efficacy endpoints will be summarized by pegloticase treatment status (On Treatment, Post-Treatment, and Overall), visit, and treatment group. On Treatment will include post-baseline visits on or after pegloticase infusions. Subjects will only be summarized in the On Treatment visits for visits that occur (and results available) while still receiving pegloticase infusions. End of pegloticase infusion visit (windowed) if one occurs, will also be considered On Treatment, as will the Week 24 visit for subjects who complete treatment and study at Week 24. Post-Treatment visits are any post-baseline visits after the end of pegloticase infusions (or Week 24/EOS if subjects complete treatment). Overall status will include all visits for all subjects regardless of pegloticase treatment status.

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 analysis summaries. 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 analysis period will not be included in the responder analysis.

10.3.1. Proportion of 5 mg/dL Responders during Month 6 (Weeks 20, 21, 22, 23 and 24)

The proportion of responders is defined as subjects achieving and maintaining sUA < 5 mg/dL for at least 80% of the time during Month 6. These will be calculated using the same method described for the primary efficacy endpoint (Section 10.2). The endpoints will be analyzed using the same methodology described in Section 10.2.

10.3.2. Change from Baseline in Mean HAQ Pain Score

The HAQ pain score will be administered at the Screening; prior to pegloticase infusion at the Day 1 and Weeks 6, 14, and 20 Visits during the Pegloticase Treatment Period; and at the End of Pegloticase Infusions Visit (if applicable), Week 24/End of Study/Early Termination and 3 month Post Treatment Follow-up Visits.

The HAQ pain score consists of a doubly anchored, horizontal visual analog scale (VAS) 15 cm in length, that is scored from 0 (no pain) to 100 (severe pain). Subjects are asked to rate the severity of the pain they have had because of illness in the past week by placing a vertical mark on the VAS. In order to convert the score to a 0-100 scale, the results (in cm) in the database will be divided by 15 then multiplied by 100.

Observed values and change from baseline in mean HAQ pain score will be summarized for each visit using descriptive statistics and 95% normal theory-based two-sided confidence interval by pegloticase treatment status (On Treatment and Overall).

10.3.3. Change from Baseline in Mean HAQ-DI Score

The HAQ-DI score will be administered at the Screening visit; prior to pegloticase infusion at the Day 1 and Weeks 6, 14, and 20 Visits during the Pegloticase Treatment Period; and at the End of Pegloticase Infusions Visit (if applicable), Week 24/End of Study/Early Termination and 3 month Post Treatment Follow-up Visits.

The HAQ-DI is a self-report functional status instrument that can be filled out by a subject in less than 5 minutes and requires 1 minute to score. The index measures disability over the past week by asking a total of 20 questions covering 8 domains of function: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. There are at least 2 questions in each domain and the 8 domains represent a comprehensive set of functional activities. The HAQ-DI is calculated by scoring the answer to each question in the HAQ from 0 to 3, with 0 representing the ability to do without any difficulty, and 3 representing inability to do. Any activity that requires assistance from another individual or requires the use of an assistive device raises a 0 or 1 score to a 2. The highest score for each of the 8 domains is summed (range from 0 to 24) and divided by 8 to yield, on a scale with 25 possible values, a Functional Disability Index with a range from 0 to 3.

If a domain has all responses missing (including aids/devices) then the domain is considered missing. If some of the questions have a result and/or the aids/devices is checked, then use available values to calculate a domain score. The disability index is based on the number of domains answered and is computed only if the subject completes answers to at least 6 domains [Bruce and Fries, 2003]. That is, if 6 domains are non-missing, then the average of the 6 available scores will determine the Functional Disability Index. If < 6 domains are non-missing then the HAQ-DI score will be missing.

If "Other" option is checked in either of the "AIDS AND DEVICES" sections of the questionnaire, the corresponding "Other, Specify" field will be reviewed and categorized by Horizon Therapeutics into an appropriate domain of function, so it can be incorporated into the score.

Observed values and change from baseline in mean HAQ-DI score will be summarized for each scheduled visit using descriptive statistics and 95% normal theory-based two-sided confidence interval by pegloticase treatment status (On Treatment and Overall).

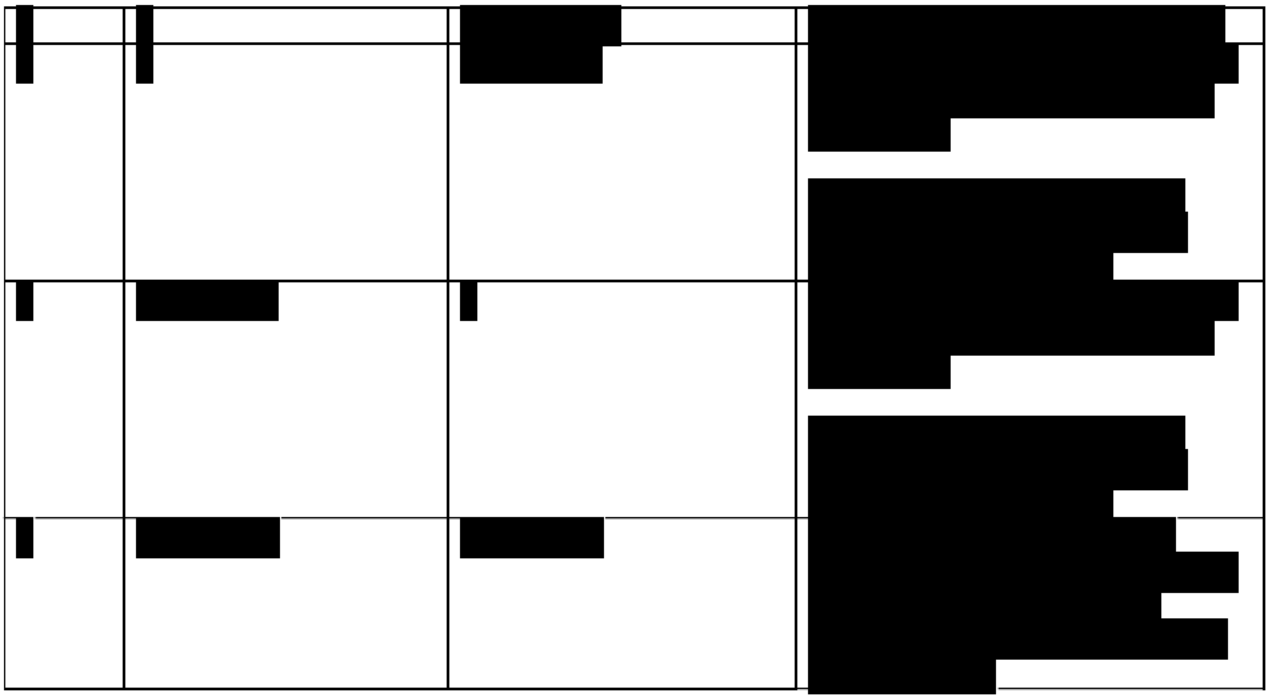
10.4. [redacted]

10.4.1. [redacted]

[redacted]

10.4.2. [redacted]

[redacted]



10.4.3. [redacted]

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10.4.4. [redacted]

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10.4.6. [redacted]

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If any single tophus shows progression, or if a new tophus appears during the study (as identified on the [redacted]

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[redacted]	[redacted]
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[redacted]	[redacted]

[redacted]

10.4.7. [redacted]

[redacted]

10.4.8. [redacted]

[redacted]

[redacted]

MAP will be calculated from SBP and DBP as MAP = 1/3 * SBP + 2/3 * DBP.

Observed values and mean change from baseline in SBP, DBP and MAP at each visit will be summarized using descriptive statistics and 95% normal theory-based two-sided confidence interval. Line plots by visit for mean SBP, mean DBP, mean CFB (change from baseline) in SBP, and mean CFB (change from baseline) in DBP will be provided.

10.4.10. [redacted]

10.4.11. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.4.12. [redacted]

[redacted]

10.4.13. [redacted]

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10.4.14. [redacted]

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[redacted]

[redacted]

10.4.15. [redacted]

[redacted]

[redacted]

[redacted]

11. Pharmacokinetics and Anti-drug Antibody Analysis

Serum samples for PK analysis of pegloticase will be collected after the end of infusion on Day 1 (prior to discharge); prior to the pegloticase infusion and after the end of the infusion (prior to discharge) at Weeks 2, 6, 14, and 22. Additional PK samples will be collected at the Week 21 Visit, the End of Pegloticase Infusions Visit (if applicable), and the Week 24/End of Study/Early Termination Visit.

Concentrations for pegloticase will be summarized using descriptive statistics by scheduled timepoint for the PK population.

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

- A listing including subject, week/time point (actual, planned), treatment and serum concentrations. End of infusion sampling times are expressed relative to the start time of infusion.
- A table summary of serum pegloticase concentrations at each time point (n; mean, SD, coefficient of variation (CV)% calculated as 100% × SD/mean, minimum, 25th percentile, median, 75th percentile and maximum) for the PK Population.

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

Serum samples for evaluation of anti-PEG and anti-uricase IgG antibodies will be collected prior to the pegloticase infusion on Day 1 and at the Week 2, 6, 14, 22 Visits, the End of Pegloticase Infusions Visit (if applicable), the Week 24/End of Study/Early Termination Visit, and the 3 month Post Treatment Follow-up Visit. In the event of an AE suspected to be an infusion reaction, a serum sample will be collected in a serum separating tube at that time or at the subsequent visit for future evaluation of pegloticase antibodies.

Using the ITT Population for anti-PEG IgG antibodies, the number and percentage of subjects with ADA positive at baseline, ADA negative at baseline, ADA positive at post-baseline but negative at baseline or with increase in titer from baseline, ADA positive at post-baseline but negative at baseline, subjects with increase in titer from baseline who were ADA positive at baseline, and ADA negative or subjects with no increase in titer from baseline will be summarized by scheduled timepoint. Similarly for anti-uricase IgG antibodies, the number and percentage of subjects with ADA positive at baseline and post-baseline will be summarized by scheduled timepoint.

Kaplan-Meier estimates of the time to positive anti-PEG, and positive anti-uricase with 25th percentile, median, 75th percentile, and 95% CI, along with a Kaplan-Meier curve will be produced. Further, the mean and coefficient of variation (CV%) of antibody titers (for samples confirmed positive) will be provided by visit and time point.

Further, the mean and CV% of pegloticase concentrations will be provided by visit in the subset of subjects who are ADA positive (defined as positive for anti-PEG or anti-uricase antibodies) and ADA negative (defined as negative for both anti-PEG and anti-uricase antibodies) for each visit. This analysis will be provided for the ITT Population.

12. Safety

Safety analyses will be based on the safety population.

Safety will be assessed via AEs including AEs of special interest (i.e., IRs, anaphylaxis, gout flares, and cardiovascular events), concomitant medication use (refer to Section 9.4), physical examinations, vital signs, clinical safety laboratory evaluations (complete blood count, chemistry, urine albumin:creatinine ratio), pregnancy testing (if applicable), electrocardiograms (ECGs), and biopsy confirmed renal rejection.

All safety information will be provided in subject listings.

12.1. Extent of Exposure

Study drug exposure will be summarized using the duration of treatment (in days), number of doses, and total dosage received for pegloticase. Interruptions in pegloticase infusions will be summarized. Reasons for infusion interruptions will be provided in the listings.

For the Pegloticase Treatment Period, the following will be summarized:

- Pegloticase
  - Number of pegloticase infusions received overall (summarized with frequency summary along with descriptive statistics of mean, SD, median, minimum, and maximum)
  - Duration in days between first and last pegloticase infusion, defined as last infusion date – first infusion date + 1 (summarized with descriptive statistics of mean, SD, median, minimum and maximum)
  - Number of incomplete infusions received (summarized with frequency summary along with descriptive statistics of mean, SD, median, minimum and maximum)
  - Number of interrupted infusions (summarized with frequency summary along with descriptive statistics of mean, SD, median, minimum and maximum)
- At each scheduled Pegloticase infusion visit
  - Number of subjects receiving a complete infusion (i.e. full dose administered)
  - Number of infusions administered without interruption
  - Number of subjects with an interrupted infusion

The usage of prophylaxis treatments (IR prophylaxis usage of fexofenadine in the evening prior to pegloticase infusion, IR prophylaxis of fexofenadine, acetaminophen, and methylpredisone on the morning prior to pegloticase infusion) will be provided in listings only.

12.2. Treatment Compliance

Other than the summarizations of pegloticase infusions described in Section 12.1, the compliance with pegloticase will not be summarized.

12.3. Adverse Events

All adverse events will be coded using MedDRA version 20.1. AE monitoring will begin from the signature of the Informed Consent Form (ICF) until the 3 month Post Treatment Follow-up Visit. SAE monitoring will begin from the signature of the ICF until the 3 month Post Treatment Follow-up Visit.

12.3.1. Definition of Period of Onset

- Non-treatment-emergent events:

- Adverse events with an onset date and time strictly prior to the first pegloticase treatment.

- Treatment-emergent adverse events (TEAEs):
  - Adverse events that occur on or after the start date and time of the first pegloticase infusion through 30 days after the last dose of pegloticase.

- Adverse events in the follow-up period:
  - Adverse events with an onset date more than 30 days after the last dose of pegloticase.

Missing data conventions for AEs are described in Section 8.3.2. The imputed onset dates will be used to determine the period of onset.

12.3.2. Presentation of Results

All AEs, both serious and non-serious, will be assessed for severity using the Rheumatology Common Toxicity Criteria (CTC) v2.0. Summaries of TEAEs will be for the safety population.

An overall summary of TEAEs will be provided, 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 pegloticase
- Serious TEAEs related to pegloticase
- TEAEs with a Rheumatology CTC Criteria of 3 or higher
- TEAEs leading to permanent withdrawal of pegloticase
- TEAEs related to pegloticase leading to permanent withdrawal of pegloticase
- TEAEs leading to death
- TEAEs of special interest

Using the safety population, an overall summary of AEs occurring during the follow-up period (with onset more than 30 days after the last dose of study medication), including the number and percentage of subjects with each AE type as well as the number of events for each of the following:

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

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

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

- TEAEs overall and by SOC and PT for the: Pegloticase Treatment Period and Follow-up Period
- TEAEs by maximum severity, overall and by SOC and PT for the Pegloticase Treatment Period
- TEAEs related to pegloticase overall and by SOC and PT for the Pegloticase Treatment Period
- TEAEs related to pegloticase by maximum severity, overall and by SOC and PT for the Pegloticase Treatment Period
- Serious TEAEs, overall and by SOC and PT for the: Pegloticase Treatment Period and Follow-up Period
- TEAEs leading to permanent withdrawal of pegloticase, overall and by SOC and PT for the Pegloticase Treatment Period

The incidence per person years of exposure to pegloticase will be provided on all tables except those summarizing events by maximum intensity, and those for the post-treatment follow-up period.

Person years of exposure to pegloticase is defined as [(last treatment date in the period– first treatment date in the period + 1)/365.25].

For summaries by SOC, PT, and maximum severity, a subject will only be counted once for each SOC based on the maximum intensity level reported for that SOC and once for each unique PT within that SOC level at the maximum intensity level reported for that PT. For summaries by SOC and PT only, a subject will be counted at most once at the SOC level and at most once at each unique PT within the SOC level. Summaries presenting the frequency of TEAEs by SOC and PT will be ordered alphabetically by SOC and then, within a SOC, alphabetically by PT.

In addition to the listing of all AEs, separate listings will be provided for serious AEs, AEs leading to withdrawal of pegloticase, AEs leading to study discontinuation, AEs of special interest, and AEs leading to death. TEAEs and the period of onset will be identified on each listing. A listing of any subject with an interruption in treatment of pegloticase due to COVID-19 will be created which will identify AEs as pre-interruption, during interruption, or post-interruption.

12.3.3. Adverse Events of Special Interest

Adverse events of special interest will include: infusion reactions (IRs), anaphylaxis, gout flares, and cardiovascular events. An external adjudication committee will adjudicate the AESIs of IR, anaphylaxis and cardiovascular events.

12.3.3.1. *Infusion Reactions (IRs) and Anaphylaxis*

An IR will be defined as any infusion-related AE or cluster of temporally-related AEs, not attributable to another cause, which occur during the pegloticase infusion and for up to 2 hours post infusion. Other AEs that occur outside of the 2-hour window following the infusion may also be categorized as an IR at the PI's

discretion. Signs and symptoms of the IR and treatments administered will be documented in the medical record and in the eCRF, and will be adjudicated.

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

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

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives; pruritus or flushing; urticaria, and angioedema (of lips, tongue, or uvula) and ≥ 1 of the following:
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia); and
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue, uvula);
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia);
   c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence); and
   d. Persistent gastrointestinal symptoms (e.g., crampy, abdominal pain, vomiting).
3. Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours): systolic blood pressure <90 mmHg or >30% decrease from that subject's baseline.

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

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

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

Both the investigator-reported and adjudicated events and the associated signs and symptoms, will be summarized separately by SOC, PT, severity, and the time relative to the most recent pegloticase infusion for each category above.

Time relative to the most recent pegloticase infusion will be categorized as: during infusion, ≤ 2 hours after infusion, > 2 hours to 24 hours after infusion, and > 24 hours after infusion. If the time of the infusion reaction or anaphylaxis is missing, the category will be assigned as "Missing".

Serious events and the associated symptoms will be summarized by SOC and PT for each category.

The number of events per subject, the number of events and serious events per infusion, and the number of subjects with the first event by infusion number will be summarized as well for each category. IRs (including anaphylaxis) that occur on the same date will be considered one event.

Time to first infusion reaction or anaphylaxis (Kaplan-Meier analysis) will be plotted. Time to first infusion reaction or anaphylaxis for subjects who experience infusion reaction or anaphylaxis (continuous variable descriptive stats) will be summarized. Summaries of events will be tabulated only if 5 or more subjects have either an event adjudicated as an IR or anaphlyaxis or any events in the database identified as IRs or anaphylaxis.

12.3.3.2. *Cardiovascular Events*

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

Any MACE including Non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure.

- For cardiovascular death:
    - Standardized MedDRA Queries (SMQ): Myocardial infarction, Ischaemic Central Nervous System (CNS) Vascular conditions; Haemorrhagic central nervous system vascular conditions, Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic, Embolic and thrombotic events (arterial, venous, vessel type unspecified and mixed arterial and venous), Cardiac failure, shock-associated conditions, Torsade de pointes/QT prolongation, Arrhythmia related investigations, signs and symptoms, Cardiomyopathy, Supraventricular tachyarrhythmias (narrow), Ventricular tachyarrhythmias (narrow), Conduction defects
    - All PTs under SOC of Cardiac disorders
    - HLGT Aneurysm
- For non-fatal myocardial infarction: SMQ Myocardial infarction
- For non-fatal stroke: SMQ: Ischaemic Central Nervous System (CNS) Vascular conditions; Haemorrhagic central nervous system vascular conditions; Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic
- Congestive heart failure: SMQ Cardiac failure

Cardiovascular events will be tabulated only if 5 or more subjects have experienced a cardiovascular event or have an event adjudicated as a cardiovascular event. Using the safety population, cardiovascular events will be summarized by MedDRA SOC and PT, adjudicated as well as any identified by investigator.

12.3.3.3. *Gout Flares*

It is common for potent ULTs to lead to acute attacks of gout. Gout flares will be confirmed through questioning the subject or direct observation by the Investigator and will be recorded as AEs.

The number of gout flares (recorded in the AE eCRF) per subject will be summarized using the safety population. These events will be further summarized by month of occurrence. A month is defined as 30 days. Events are summarized for each month according to the onset date of the flares, and only summarized in the month of onset. For month 1, percentages will be based on the number of subjects in

the safety population. For the other months of the pegloticase treatment period, percentages will be based on the number of subjects who had follow-up at least through the start of the period-specific time period. Subject self-reported gout flare assessment will also be summarized. The 30 days following the end of treatment are included in the follow-up time period.

Percentages will be calculated using the number of subjects in the safety population having follow-up through the beginning of the respective month.

12.4. Laboratory Evaluations

Blood (for hematology and clinical chemistry) will be collected at Screening, prior to the pegloticase infusion on Day 1 and at the Week 2, 6, 14, and 22 Visits, the End of Pegloticase Infusions Visit (if applicable), the Week 24/End of Study/Early Termination Visit and 3 month Post Treatment Follow up Visit.

Urine (for albumin:creatinine ratio) samples will be collected at Screening, prior to the pegloticase infusion on Day 1 and at the Week 6, 14, and 22 Visits, the End of Pegloticase Infusions Visit (if applicable) and Week 24/End of Study/Early Termination Visit.

Urine (for human chorionic gonadotropin) samples will be collected at selected visits.

Safety laboratory assessments will include:

- Hematology: complete blood count with differential (hemoglobin concentration, hematocrit, erythrocyte count, platelet count, leukocyte count, and differential leukocyte count);
- Chemistry: albumin, transaminases (aspartate aminotransferase, alanine aminotransferase), alkaline phosphatase, total bilirubin, creatinine (including calculation for eGFR calculated by the Modification of Diet in Renal Disease [MDRD] study equation : 175 x $(S_{cr[mg/dL]})^{-1.154}$ x $(age)^{-0.203}$x (0.742 if female) x (1.212 if African American) or 175 x $(S_{cr[\mu mol/L]}/88.4)^{-1.154}$ x $(age)^{-0.203}$x (0.742 if female) x (1.212 if African American), glucose, sodium, potassium, calcium, chloride, total protein, blood urea nitrogen, and human chorionic gonadotropin (at the Screening Visit and the Week 24/End-of-Study/Early Termination Visit for all female subjects of childbearing potential); and
- Urine: albumin:creatinine ratio, and human chorionic gonadotropin (for all female subjects of childbearing potential).

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

Laboratory results will be displayed using the conventional units. for all summaries and listings. Clinical laboratory test results (hematology and chemistry) and their changes from baseline will be summarized by visit for the safety population using descriptive statistics by pegloticase treatment status (On Treatment, Post-Treatment, and Overall).

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

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

Using the safety population, shift tables using categories of low, normal, and high, comparing laboratory test results from baseline to each visit will be presented with percentages based on subjects with a non-missing value at baseline and post-baseline visit. For tests where the Common Terminology Criteria for

Adverse Events (CTCAE) criteria are available, shift tables will be based on the CTCAE grade. The CTCAE version 4.03 will be used for these summaries.

Analysis of allantoin will be done separately from other laboratory values.

12.5. Pregnancy Test

Pregnancy test results will be provided in a listing.

12.6. Vital Signs

Routine vital signs, including blood pressure, respiratory rate, temperature, and heart rate will be measured at Screening, Day 1 and Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, the End-of-Pegloticase-Infusions Visit (if applicable), the Week 24/End-of-Study/Early Termination Visit and the 3-month Post-Treatment Follow-up Visit (before any study drug infusion or scheduled blood draws). During the pegloticase treatment period study visits, vital signs should be taken before the pegloticase infusion and any time after the end of the infusion, but prior to subject's discharge/release from the site. In addition, if immediate infusion-associated events are noted during the infusion, vital signs will be monitored at least every 30 minutes until resolution or stabilization of the AE.

Blood pressure summaries are included in the exploratory analysis Section 10.4.9.

Weight should be measured in kilograms or pounds without shoes and recorded at the Screening Visit, prior to pegloticase infusion on Day 1, at the Week 8 and 16 Visits, the non-infusion End of Pegloticase Infusions Visit (if applicable), the Week 24/End of Study/Early Termination Visit, and the 3 month Post Treatment Follow-up Visit.

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

Descriptive summaries of observed and change from baseline values will be presented for each vital sign parameter except SBP, DBP and MAP by visit, using safety population by pegloticase treatment status (On Treatment, Post-Treatment, and Overall). Vital sign measurements that are monitored as a result of an infusion-associated event, will not be included in the descriptive summaries but will be presented in subject listings.

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

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

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

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

The following formula will be used to determine the BMI (in kg/m2) using weight [in kg] and height [in m]:

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

12.7. ECG

An electrocardiogram (ECG) will be performed at Screening and at the discretion of the Investigator thereafter. When a subject experiences an AE suspected to be an IR, a 12-lead ECG will also be performed.

The results will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated as clinically significant (CS) or not clinically significant (NCS) by the investigator.

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

- Normal
- Abnormal NCS
- Abnormal CS

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

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

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

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

ECG results will also be listed.

12.8. Physical Examination

A complete physical examination will be performed at the Screening Visit and will include assessments of head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, extremities, neurological status and musculoskeletal system, and for presence of tophi, as well as gout history and symptom severity. A targeted physical examination (for joint and skin evaluation and assessment of AEs) will be conducted based on potential risk for or occurrence of AEs at Day 1, and prior to administration of infusion at Weeks 4, 8, 12, 16, and 20, the End of Pegloticase Infusions Visit (if applicable), Week 24/End of Study/Early Termination Visit and 3 month Post Treatment Follow Up Visit; at a minimum this should include heart, lungs, and abdomen. Clinically significant findings from the targeted physical examinations will be recorded as AEs.

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

13. Interim Analyses

No formal interim analysis is planned for this study. Efficacy and safety data may be summarized periodically throughout the study to support scientific publications. Additionally, safety data will be summarized regularly for safety monitoring. Final analysis will occur when all subjects have completed the study.

No adjustments to type I error rates or nominal confidence levels for confidence intervals will be made to account for these summaries.

14. Changes from Analysis Planned in Protocol

The analysis population definitions have been changed:

- Per the protocol, only the modified Intent-to-Treat (mITT) population was defined as all subjects who receive at least 1 dose of pegloticase. The mITT population was planned to be used for analysis of ADA, efficacy and safety data.
- For the purposes of ease of future integration with other pegloticase studies, the mITT defintion has been removed, and instead has been replaced by the Intent-To-Treat (ITT) population definition (for the analysis of ADA and efficacy data) and the safety population defintion (for the analysis of safety data). Both the ITT and the safety population are defined as all subjects who receive at least 1 dose of pegloticase.

The phrasing of the safety endpoints relating to laboratory tests and vital signs has been updated from "Laboratory tests" and "Vital signs" to "Laboratory tests: change from baseline to each scheduled assessment" and "Vital signs: change from baseline to each scheduled assessment," respectively.

15. Reference List

Protocol: A Multicenter, Open-Label, Efficacy and Safety Study of Pegloticase in Patients with Uncontrolled Gout Who Have Undergone Kidney Transplantation. HZNP-KRY-406, Version 1.0.

Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes. 2003;1:20.

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

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

16. Programming Considerations

16.1. General Considerations

- All TLFs will be produced in landscape format.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color)
- Specialized text styles, such as bolding, italics, borders, and shading will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., ?). Certain subscripts and superscripts (e.g., m2, Ctrough) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

16.2. Table, Listing, and Figure Format

16.2.1. General

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

16.2.2. Headers

- All output should have the following header at the top left of each page:
- Horizon Therapeutics Ireland, DAC, Protocol HZNP-KRY-406
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

16.2.3. Display Titles

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

- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Analysis Set)

16.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

16.2.5. Body of the Data Display

16.2.5.1. *General Conventions*

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

- Alphanumeric values are left-justified;

- Whole numbers (e.g., counts) are right-justified; and

- Numbers containing fractional portions are decimal aligned.

16.2.5.2. *Table Conventions*

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

Severity Rating	N
mild	0
moderate	8
severe	3

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

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

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Everyp-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

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

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

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

16.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

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

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

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

- Units will be included where available

16.2.5.4. *Figure Conventions*

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

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

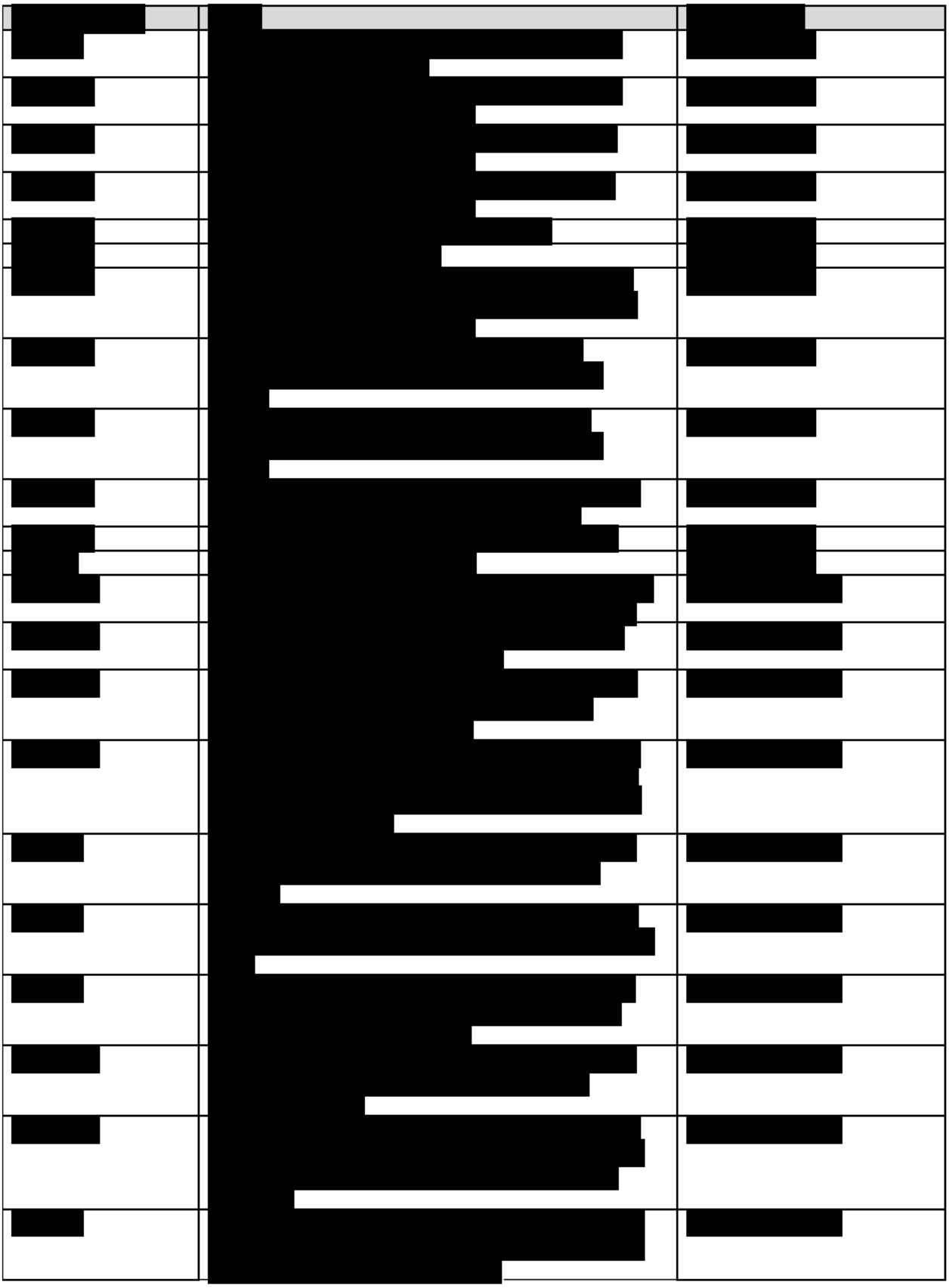
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.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

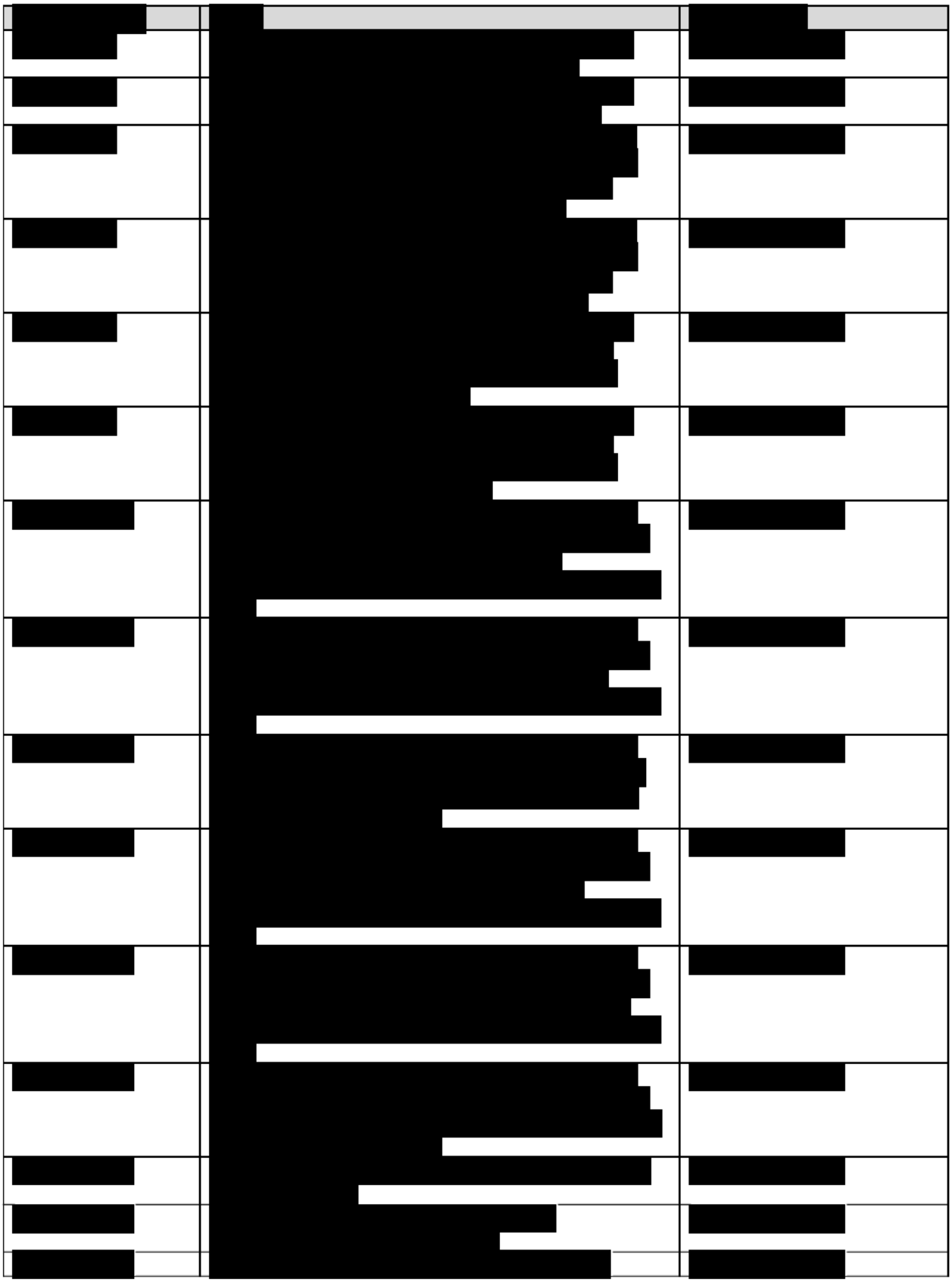
17. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses.

[redacted]

18. [redacted]





19. [redacted]

20. [redacted]