SIGNATURE PAGE

Protocol Title:	A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-release Capsules (RP103) in Patients with Cystinosis
Sponsor:	Horizon Pharma USA, Inc. 150 S. Saunders Road Lake Forest, IL 60045
Protocol Number:	RP103-04
Document Date/Version:	07August 2017 / v2.0

Cytel, Inc. Signatory:

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Cytel Inc.
955 Chesterbrook Blvd. Suite
Chesterbrook, PA 19087

Signature:_____

Date:_____

Sponsor Approval

Sponsor Signatory:

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Associate Director, Biostatistics
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150 S. Saunders Road
Lake Forest, Il 60045

Signature: [redacted]

Date: 08 AUG 2017

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Senior Medical Director
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Signature: [redacted]

Date: 08 Aug 2017

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Lake Forest, Il 60045

Signature: _____
Date: _____

STATISTICAL ANALYSIS PLAN
Protocol RP103-04
A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-released Capsules (RP103) in Patients with Cystinosis

Protocol Number:	RP103-04
(Version Date)	21 November 2010 (Original) 18 November 2015 (Amendment 9)
Name of Test Drug:	RP103
Phase:	3 Long-Term Safety / Efficacy
Methodology:	**Open label**
Sponsor:	Horizon Pharma USA, Inc. 150 S. Saunders Road Lake Forest, IL 60045
Sponsor Representative:	[redacted] Chief Medical Officer & Executive Vice President Research and Development Horizon Pharma Inc.
Document Date:	07AUG2017
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Contents

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ATC-4	Anatomical Therapeutic Chemical 4th Level
BMI	Body Mass Index
BSA	Body Surface Area
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NDS	New Drug Submission
[redacted]	[redacted]
PK	Pharmacokinetic
PD	Pharmacodynamic
PT	Preferred Term
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SOC	System Organ Class
[redacted]	[redacted]
WHO	World Health Organization

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

This is a long-term, single-arm, open-label study of the safety, tolerability and steady-state pharmacokinetics and pharmacodynamics of RP103 in pediatric and adult subjects with cystinosis. Subjects who will have completed the last visit of the previous phase III Study (RP103-03) have been offered the opportunity to enroll in this extension study. Additional subjects, who did not complete the RP103-03 study, may have been enrolled after completion of the analysis of the RP103-03 study where the non-inferior efficacious and safe dose of RP103 versus Cystagon® has been determined.

1.2. Objectives of Statistical Analysis

The objective of this Study is to assess the long-term safety, tolerability, pharmacokinetics and pharmacodynamics of RP103 in pediatric and adult subjects with cystinosis.

The primary objective is to assess safety and tolerability of long-term repeat dosing of RP103 in subjects with cystinosis.

Secondary objectives include assessment of steady-state pharmacokinetics (PK) and pharmacodynamic (PD) of RP103 and [redacted]

This statistical analysis plan (SAP) describes the efficacy and safety analyses that will be performed, based on the study protocol amendment 9 dated 18NOV2015. This amendment (Version 2.0) of the SAP adds details about the statistical analysis to be performed. Changes from Version 1.0 of the SAP including the following:

- updated Sponsor from Raptor Therapeutics to Horizon Pharma
- updated protocol version for study
- added a description of visit windowing and visit mapping methods
- added a description of variables to be summarized for subject disposition
- added variables to be summarized for demographics and baseline characteristics
- added a summary of protocol deviations
- added details for pharmacokinetic and pharmacodynamics summaries
- [redacted]
- added a summary of study drug exposure
- added details for adverse event summaries
- added details for summaries of other safety parameters including labs (added shift tables), ECG, vital signs, and concomitant medications

Any changes from the SAP will be described in the clinical study report (CSR).

2. STUDY DESIGN

2.1. Synopsis of Study Design

This is a long-term, open-label study of the safety, tolerability and steady-state pharmacokinetics and pharmacodynamics of RP103 in pediatric and adult subjects with cystinosis. Initially only subjects who completed the previous phase III Study (RP103-03) will be offered the opportunity to enroll in this extension Study.

Additional subjects, who did not complete Study RP103-03 but qualify for RP103-04 based on current inclusion and exclusion criteria, may be enrolled after completion of the analysis of the RP103-03 study where the non-inferior efficacious and safe dose of RP103 versus Cystagon® has been determined.

Study visits consist of:

For subjects who completed Study RP103-03:

- Screening Visit: The RP103-04 Screening visit occurred simultaneously with the RP103- 03 Period 2 Day 7 End of Study (EOS) visit. These subjects continued RP103 Q12H treatment at the last dose level prescribed during their participation in Study RP103- 03.

- Monthly Study Visits are only for subjects who completed Study RP103-03 and began within 1 month (± 7 days) after study entry. Each subject completes a minimum of six (6) consecutive monthly visits.

- Quarterly Study Visits commence for each subject ≥ 1 month and < 4 months after the subject has completed at least six (6) consecutive Monthly visits. Each Quarterly visit takes place by the middle of the first month (± 7 days) of each calendar quarter (i.e. January 15, April 15, July 15 and October 15).

- End of Study (EOS) Visit is conducted within 7 (± 2) days from the last completed study visit or from the date of decision to terminate.

For subjects who did not complete Study RP103-03:

- Screening Visit which may occur up to 28 days prior to Day 1.

- Dose Confirmation Period (Days 1-5) which includes three (3) study visits over five (5) days.
    - Day 1 includes a morning study visit while the subject is fasted, with pre-dose blood samples collected for trough cysteamine and peak white blood cell (WBC) cystine determination while the subject is still taking Cystagon®. RP103 treatment regimen begins at the clinic on the morning of Day 1, administered Q12H at a starting total daily RP103 dose equal to 70% of the Screening total daily Cystagon® dose. Subjects leave the clinic for Days 2-3 and take RP103 as instructed.
    - Days 4 and 5 each include a morning study visit; RP103 Q12H treatment regimen continues.

- Quarterly Study Visits commence for each subject ≥ 1 month and < 4 months after enrollment in the study. Each quarterly visit takes place by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15).

- End of Study (EOS) Visit will be conducted within 7 (± 2 days) from the last completed study visit or from the date of decision to terminate.

2.2. Randomization Methodology

This is a single-arm study. Subjects are not randomized.

2.3. Stopping Rules and Unblinding

This is an open-label, long-term safety study with no stopping rules.

2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1.1 and Table 1.2.

Table 1.1 Schedule of Events (All Subjects)

Procedure	Screening[a]	Dose Confirmation Period		Visit Frequency		End of Study[f]
Study Visit	**Day -28 to -1**	**Day 1[b]**	**Day 4 and Day 5**	**Monthly[d] (± 7 days)**	**Quarterly[e] (± 7 days)**	**7 (± 2) days after last visit, or decision to terminate**
Number of Study Visits	**1**	**1**	**2**	**6 to 9**	**5 to 6**	**1**
Informed Consent	X					
Inclusion/Exclusion	X	X[c]				
Demographics	X[g]					
Medical History	X[g]	X[c]				
Medication History	X[g]	X[c]				
Menstrual Cycle History (females of child-bearing potential only)	X[g]	X[c]				
Serum Pregnancy Test (females with childbearing potential only)	X	X[c]		X	X	
Body height	X	X[c]		X	X	X
Body weight	X	X[c]		X	X	X
BMI calculations	X	X[c]		X	X	X
BSA calculations	X	X[c]		X	X	X
Physical Examination[i]	X[h]	X[c]		X	X	X
Clinical Laboratory Test: Hematology, Chemistry, Urinalysis[j]	X[h]	X[c]		X	X	X
ECG[k]	X[h]	X[c]		X	X	X
Vital signs[l]	X[h]	X	X	X	X	X
[redacted]	X	X[c]		X	X	X
[redacted]	X	X[c]		X	X	X
Daily diary: training	X					
Daily Diary: medications	X	X		X	X	

Daily Diary: collection		X		X	X	X
Food/liquid intake control[s]		X[c]	X	X	X	X
Q12H RP103 administration[o]	X[h]	X	X	X	X	
WBC Cystine (PD) sample collection[p] collection	X	X[c]	X (post-dose)	X	X	X
Cysteamine (PK) sample collection[q]	X	X	X (post-dose)	X	X	X
Investigator Review of Safety and PK/PD data[r]			X	X	X	
Concomitant medications	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X

a. For subjects completing Study RP103-03, Screening can be performed concurrent with the RP103-03 End of Study Visit and will be considered Day -1 for this Study. For subjects that did not participate in the RP103-03 study, Screening can take place up to 28 days prior to the first Study visit (Day 1).
b. Day 1 Visit is only to be performed for subjects that did not complete Study RP103-03.
c. These procedures were should have been performed at Screening and are to be repeated only if the Day 1 visit occurs more than 7 days after the Screening visit.
d. A minimum of 6 consecutive Monthly (± 1 week) Visits will be conducted for all subjects who completed Study RP103-03 prior to enrolling in study RP103-04. Subjects who did not complete Study RP103-03 will not attend Monthly visits.
e. Quarterly visits will take place by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15) so that samples can be analyzed on the bioanalytical lab's quarterly analysis schedule.
f. The End of Study visit will be conducted within 7 (± 2 days) from the last completed study visit or from the date of decision to terminate.
g. For subjects that completed the RP103-03 Study, data can be obtained from the RP103-03 Screening visit.
h. For subjects that completed the RP103-03 Study, data can be obtained from the RP103-03 End of Study Visit.
i. Physical examinations are to include standard physical assessments together with a neurological and skin examination.
j. Clinical laboratory (chemistry and hematology) and urinalysis samples will be collected at Screening (if required) and at Monthly and Quarterly visits, thereafter and at the End of Study (EOS) visit.
k. 12-lead ECG will be collected within 30 minutes prior to Study drug administration at Screening (if required) and at Monthly and Quarterly visits, thereafter and at the End of Study (EOS) visit. For subjects that did not complete Study RP103-03, the 12-lead ECG will also be conducted at approximately 3 hours (± 15 minutes) post RP103 dose on Day 1.
l. Vital signs will be measured within 30 minutes prior to Study drug administration at Screening (if required) and at Monthly and Quarterly visits, thereafter and at the End of Study (EOS) visit. For subjects that did not complete Study RP103-03, vital signs will also be repeated 30 minutes prior to Study drug administration on Day 1.

[redacted]

s,

o. RP103 will be administered Q12H daily. Subjects that completed Study RP103-03 will continue to receive their Q12H RP103 dose determined during that Study. For subjects that did not complete Study RP103-03, the first dose of RP103 will be given on Day 1, with a starting Q12H RP103 dose at a total daily dose which is 70% of their total daily dose Cystagon® dose.
p. A PD (WBC cystine) sample will be collected at: Screening, (if subject did not complete Study RP103-03) at 5-6 hours after the last Cystagon® dose, on Day 1 (if subject did not complete Study RP103-03) immediately prior (≤ 15 minutes) to morning dose administration of RP103, and for all subjects at 0.5 hour (30 minutes) post RP103

dose on Monthly and Quarterly Visits, thereafter and at the End of Study (EOS) visit. For subjects who have transitioned back to Cystagon®, the EOS visit PD blood sample will be collected immediately prior to their next Cystagon® dose.

q. A PK (plasma cysteamine) sample will be collected at: Screening (if subject did not complete Study RP103-03) at 5-6 hours after the last Cystagon® dose, on Day 1 (if subject did not complete Study RP103-03) immediately prior (≤ 15 minutes) to morning dose administration of RP103, and for all subjects at 0.5 hour (30 minutes) post RP103 dose on Monthly and Quarterly Visits, thereafter and at the End of Study (EOS) visit. For subjects who have transitioned back to Cystagon® PK blood sample at the EOS visit will be collected immediately prior to their next Cystagon® dose.

r. Investigator will perform a review of available safety, PK and PD date prior to or at study visits (i.e., Monthly/Quarterly). A dose adjustment may be indicated, as described in Section 8.5of the protocol. For subjects who did not complete Study RP103-03, the first potential dose adjustment should be as soon as the Investigator receives WBC cystine results for the Dose Confirmation Period, so that any RP103 dose adjustment may be implemented before the subject returns for their next study visit (Quarterly Visit 1).

s. Food should try to avoid eating food for at least 2 hours before and 30 minutes after RP103 administration. In case subjects cannot comply with this recommendation, they should ingest at least a small amount of food around the time of RP103 dosing (from 1 hour before to 1 hour afterwards).

[redacted]

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

[redacted]

[redacted]

2.5. Study Endpoints

2.5.1. Safety Endpoints

The safety profile of RP103 is investigated by safety reviews conducted by the Investigator at or prior to each monthly or quarterly visit and through adverse event report monitoring (including attribution of treatment-emergent adverse events and serious adverse events [SAEs]), physical examination (including basic neurological and skin assessment findings), vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory testing as outlined in the Schedule of Events.

2.5.2. Pharmacokinetic Endpoints

The trough plasma cysteamine concentration is measured from samples collected 0.5 hour post dose at each study visit.

2.5.3. Pharmacodynamic Endpoints

The WBC cystine content is measured from samples collected 0.5 hour post dose at each study visit.

[redacted]

3. SUBJECT POPULATIONS

3.1. Population Definitions

Two populations for this study are planned for analysis as described below.

Safety Population: The Safety Population consists of all subjects who received at least one dose of study drug (RP103).

PK/PD Population: All subjects who have at least one PK/PD measurement are included in the PK/PD population.

Each one of these 2 populations is then partitioned in 3 subpopulations:

A: Subjects who completed Study RP103-03

B: Subjects $\leq$ 6 years old

C: Renal Transplant subjects

3.2. Protocol Violations/Deviations

Failure to meet any inclusion or exclusion criteria (see Sections 7.1 and 7.2 of the protocol) during participation in the study constitutes a protocol violation. Other unforeseen situations may result in a protocol violation and is reported accordingly. No protocol violations are used to exclude subjects from the safety analysis.

4. STATISTICAL METHODS

4.1. Sample Size Justification

The sample size for this study is determined by the number of subjects who participated in the previous phase III Study (RP103-03) and any additional subjects, who did not complete the RP103-03 study, who enroll after all subjects that participated in RP103-03 completed and data have been analyzed.

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

All data displays and analyses will adhere to the International Conference on Harmonisation (ICH) recommendations, and will be formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, N, the mean, median, standard deviation, minimum and maximum values

will be presented.

Relative days will be calculated relative to the first dose of study drug. Day 1 will be the first day of study drug administration in the study, and the day prior to the first dose of study drug administration will be Day -1. There will be no Day 0.

Any statistical testing will be considered exploratory; two-sided p-values will use alpha = 0.050.

Baseline is defined, unless otherwise specified, as the last non-missing measurement before the first dose of study drug, unless otherwise specified. For subjects who completed Study RP103-03, baseline results could come from the Screening Visit (which is the RP103- 03 Period 2 Day 7 End of Study (EOS) visit).

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.2 or later), unless otherwise noted. Medical history and adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 13.0. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (June 2010).

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates

There are no planned adjustments for covariates in this study.

4.2.5. Multiple Comparisons/Multiplicity

No formal statistical adjustments are planned for multiplicity.

4.2.6. Subpopulations

Data will be summarized by the subpopulations described in Section 3.1:

A: Subjects who completed Study RP103-03

B: Subjects ≤ 6 years old

C: Renal Transplant subjects

4.2.7. Withdrawals, Dropouts, Loss to Follow-up

There are no planned exclusions due to withdrawals, dropouts, or loss to follow-up.

4.2.8. Missing, Unused and Spurious Data

Imputation of missing data is not planned.

4.2.9. Visit Windows

The visit schedule in Study RP103-04 differed according to whether a subject entered the study after completing Study RP103-03 or entered the study without having previously participated in Study RP103-03 (i.e., Subjects ≤ 6years of age and kidney transplant recipients). This difference in visit schedule resulted in each Quarterly visit for subjects from Study RP103-03 occurring, on average, approximately 6 months later in the study than the corresponding Quarterly visit for subjects who did not previously participate in Study RP103-03. For example, the Quarterly 1 visit of a subject from Study RP103-03 generally occurred at approximately 0.75 years in the study, while the Quarterly 1 visit for a subject not previously participating in Study RP103-03 generally occurred at approximately 0.25 years in the study. Two approaches were taken in the analysis to aligning visits for summarization over time:

1. **Collected Visits**: Scheduled Visits (i.e., the visit as recorded on the case report form) were assigned to what is referred to as "Collected Visits" (see
2. Table 2). Summarization using Collected Visits will help to address the approximate 6-month difference between the Quarterly visits for subjects from Study RP103-03 compared to subjects who had not participated in Study RP103-03.

Table 2: Definition of "Collected Visits" for Subjects Not Previously Participating in Study RP103-03 (Subjects ≤ 6 Years of Age and Kidney Transplant Recipients)

Scheduled Visit		Assigned "Collected Visit" (Label)
Scheduled Visit Number	Scheduled Visit Name	
14	Quarterly 1	Monthly 3
15	Quarterly 2	Monthly 6
16	Quarterly 3	Quarterly 1
17	Quarterly 4	Quarterly 2
18	Quarterly 5	Quarterly 3
19	Quarterly 6	Quarterly 4
20	Quarterly 7	Quarterly 5
21	Quarterly 8	Quarterly 6
22	Quarterly 9	Quarterly 7
23	Quarterly 10	Quarterly 8
24	Quarterly 11	Quarterly 9

Scheduled Visit		Assigned "Collected Visit" (Label)
Scheduled Visit Number	**Scheduled Visit Name**	
25	Quarterly 12	Quarterly 10
26	Quarterly 13	Quarterly 11
27	Quarterly 14	Quarterly 12
Continues in this pattern for however many Quarterly visits occur		

The table only displays Collected Visits for which the name/label differs from that of the Scheduled Visit.

3. **Analysis Visits**: Based on the assessment date, the Study Day of each visit of a given subject (where Study Day 1 is the first day of dosing with RP103 in Study RP103-04) will be assigned to the Study Month in which it occurred, based on a window around a scheduled timepoint) . This approach of summarizing by month is referred to as summary based on "Analysis Visits." Because visits were generally scheduled quarterly rather than monthly, there may be more fluctuation in sample sizes over time for Analysis Visits than for Scheduled or Collected Visits. Details of the windowing are below.

The following time windows will be used to assign an assessment, including unscheduled assessments, to a month.

Visit	Scheduled Study Day	Time Window
Month 1	30	> 1 - ≤ 45
Month 2	60	> 45 - ≤ 75
Month 3	90	> 75 - ≤ 105
Month 4	120	> 105 - ≤ 135
Month 5	150	> 135 - ≤ 165
Month 6	180	> 165 - ≤ 195
Month 7	210	> 195 - ≤ 225
Etc.		

If more than one assessment is included in a time window, then the assessment performed closest to the Scheduled Study Day will be used in analyses. When more than one day is of equal proximity to the Scheduled Study Day, then the data collected after the Scheduled Study Day will be used in analyses.

[redacted]

4.3 Interim Analyses

There have been three interim analyses performed to support interim CSRs. The first interim CSR was dated 14 February 2012 (amended 10 January 2013). A second interim CSR was dated 17 September 2013 (amended 06 March 2015). The third interim CSR was dated 11 November 2015.

5. SUBJECT DISPOSITION

Subject disposition will be tabulated overall and for each subpopulation. The number of subjects screened and in each analysis population will be summarized. The number and percentage of subjects who complete the study will be summarized, along with the number and percentage of subjects who do not complete the study for each discontinuation reason as specified on the eCRFs.

6. PROTOCOL DEVIATIONS

The number and percentage of subjects who have major protocol deviations during the study will be summarized overall and for each deviation reason for the Safety Population.

Protocol deviations will be presented by subject in a data listing.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics at study entry will be summarized by subpopulation and overall for the Safety Population.

Variables to be summarized are:

- Continuous variables
  - Age (years)
  - Weight (kg)
  - Height (cm)
  - Body mass index (BMI) (kg/m^2)
  - Body surface area (BSA) (m^2)
  - Previous daily dose of Cystagon ($mg/m^2/day$)
  - Total daily dose of RP103 (average % of previous Cystagon dose)
  - WBC cystine level (nmol ½ cystine/mg)
- Categorical variables
  - Age category (young child, child, adolescent, adult)
  - Gender
  - Race

- Ethnicity
- WBC cystine levels (≤ 1, > 1 to ≤ 2, > 2 nmol ½ cystine/mg)

For subjects who completed study RP103-03, baseline height is taken from the RP103-03 Screening Visit. For subjects who did not complete study RP103-03, baseline height is the last available observation prior to the first dose of study drug in RP103-04. For all other parameters, baseline is as defined in Section 4.2.1.

Medical history information will be summarized by MedDRA system organ class (SOC) and preferred term (PT) by subpopulation and overall for the Safety Population.

8. PHARMACOKINETIC, PHARAMCODYNAMIC AND [redacted]

8.1. Pharmacodynamics

WBC cystine concentration levels (nmol ½ cystine/mg) will be summarized over time using descriptive statistics (number of subjects, mean, geometric mean, median, standard deviation, coefficient of variation, minimum, and maximum) for the PK/PD Population for each subpopulation and overall. Summaries will be provided for both analysis visits and collected visits. WBC cystine concentration levels will also be summarized over time by baseline WBC cystine levels (≤ 1, > 1 to ≤ 2, > 2 nmol ½ cystine/mg) for both analysis visits and collected visits.

8.2. Pharmacokinetics

Plasma cysteamine concentration (mg/L) will be summarized over time using descriptive statistics (number of subjects, mean, geometric mean, median, standard deviation, coefficient of variation, minimum, and maximum) for the PK/PD Population for each subpopulation and overall. Summaries will be provided for both analysis visits and collected visits.

[redacted]

[redacted]

complete study RP103-03, baseline is the last non-missing assessment prior to the first dose of study drug in study RP103-04.

[redacted]

[redacted]

[redacted]

9. SAFETY ANALYSES

Safety summaries will be produced for the Safety Population for each subpopulation and overall.

9.1. Study Drug Exposure

Duration of study drug exposure will be calculated as the duration from the date of first dose of RP103 in Study RP103-04 to the date of last dose as:

Exposure (days) = (Last Dose Date – First Dose Date + 1) – number of days dosed with Cystagon

Duration of exposure will be summarized for each subpopulation and overall using descriptive statistics. The number and percentage of subjects with duration of exposure in each category (≤ 12 months, > 12 months and ≤ 24 months, > 24 months and ≤ 36 months, > 36 months and ≤ 48 months, > 48 months and ≤ 60 months, and > 60 months) will also be summarized.

The mean RP103 dose (mg/m^2/day) will be summarized over time using collected visits.

9.2. Adverse Events

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0 and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term.

Summaries of adverse events will be generated for those events that are considered treatment emergent, where treatment emergent is defined as any adverse event that emerges during treatment in study RP103-04, having been absent pretreatment, or worsens relative to the pretreatment state. All adverse event summaries will be presented for each subpopulation and overall.

An overview summary table of AEs will be presented including the number and percentage of subjects reporting a treatment-emergent AE for the following categories:

- Subjects reporting at least one AE
- Subjects reporting at least one treatment-related AE
- Subjects reporting at least one serious AE (SAE)

- Subjects reporting at least one Grade ≥ 3 AE
- Subjects reporting at least one AE leading to discontinuation of study

The number and percentage of subjects who experienced at least one AE will be summarized overall and for each SOC and each PT. The percentage will be based on the number of subjects in the Safety Population. Each subject will contribute at most one count per summarization category. In other words, if a subject has more than one AE with same PT, the subject will be counted only once for that PT. Similarly, if a subject has more than one AE for a SOC, the subject will be counted only once in that SOC and PT. SOCs (and PTs within each SOC) will be sorted in summary tables by descending frequency of each.

Similarly, the number and percentage of subjects with any treatment-emergent SAEs, with any treatment-emergent adverse events assessed by the Investigator as related to treatment, and with any treatment-emergent adverse events leading to discontinuation of study and with any SAE will be summarized by SOC and PT.

The number and percentage of subjects with any treatment-emergent adverse events will be summarized by relationship to study drug (not related, unlikely related, possibly related, probably related, definitely related, unknown) and severity (mild, moderate, severe, life-threatening, death, unknown) by SOC and PT. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes – e.g. worst grade, per subject, per toxicity.

In addition, summaries of the incidence of subjects with AEs, and SAEs, by study year of onset (Year 1, Year 2 and Year 3 or later) will be generated. Treatment-emergent gastro-intestinal adverse events, i.e. adverse events with SOC of "gastrointestinal disorders", will also be summarized by frequency of episodes (1-3 occurrences vs 4 or more) by PT. Similarly, treatment-emergent treatment-related gastro-intestinal adverse events will be summarized.

All adverse events occurring on study will be listed in subject data listings.

By-subject listings also will be provided for the following: serious adverse events, adverse events for laboratory abnormalities, and adverse events leading to study discontinuation.

9.3. Laboratory Data

Clinical laboratory values will be expressed using SI units.

Hematology, chemistry, and urinalysis results will be summarized for each lab parameter at baseline, each collected postbaseline visit, and change from baseline using descriptive statistics (number of subjects, mean, median, SD, and minimum and maximum values). In the event of repeat values, the last non-missing value per visit, per timepoint will be used. If there are multiple records for the same visit and timepoint, the average of the values will be used.

Analysis of individual subject changes will be summarized by shift tables, which will be generated for hematology and serum chemistry parameters. These tables will show the number of subjects who had values that shifted from low, normal, or high at baseline to low, normal, or

high at each collected visit.

All laboratory data will be provided in data listings. Values outside of the reference range will be flagged.

9.4. Vital Signs and Physical Examinations

Vital signs data will include temperature, respiratory rate, weight, BMI, BSA, systolic and diastolic blood pressures (BPs) and heart rate. Results will be summarized at baseline, each collected postbaseline visit, and change from baseline using descriptive statistics (number of subjects, mean, median, SD, and minimum and maximum values). For subjects who completed study RP103-03, baseline height is taken from the RP103-03 Screening Visit. For subjects who did not complete study RP103-03, baseline height is the last available observation prior to the first dose of study drug in RP103-04.

By-subject listings of vital sign measurements and physical examinations will be presented in data listings.

9.5. Electrocardiogram

Electrocardiogram data will include heart rate, QRS duration, QRS axis, QT and PR intervals, and QT interval corrected for heart rate using Fridericia method (QTcF). ECG data will be summarized for baseline, each collected postbaseline visit and for the change from baseline to each visit using descriptive statistics (number of subjects, mean, median, SD, and minimum and maximum values) by treatment.

Overall interpretation results for the ECG are classified into 1 of 3 categories: normal, abnormal – not clinically significant, or abnormal – clinically significant. Shift tables will show the number of subjects who had results that shifted from normal, abnormal – not clinically significant, or abnormal – clinically significant at baseline to normal, abnormal – not clinically significant, or abnormal – clinically significant at each collected post-baseline visit.

All ECG data for each subject will be provided in data listings.

9.6. Concomitant Medications

Concomitant medications are coded using the WHO Drug dictionary (June 2010) . Results will be summarized by Anatomic Therapeutic Class 4th level (ATC-4) and preferred name. If the 4th level term is not available, the next available level (e.g., ATC-3) will be used. All medications with a stop date prior to the first dose of study drug will be considered "prior". All medications taken on or after the first RP103 dose, regardless of the start date, will be considered "concomitant."

Gastric-acid reducing (GAR) medications were recorded on a separate eCRF from concomitant medications, and will be summarized by ATC-4 and preferred name. The number of occurrences

of each GAR medication will also be summarized by ATC-4 and preferred name. For example, if a subject has two occurrences of a given medication with different start and stop dates, each occurrence will be counted.

The use of concomitant medications and GAR medications will be included in by-subject data listings.

10. CHANGES TO PLANNED ANALYSES

The following changes from Amendment 9 of the protocol have been made:

- [redacted]
- Use of gastric acid reducing medications was changed from an exploratory endpoint (per the protocol) to a safety endpoint.
- Analysis of annualized exposure adjusted AEs will not be performed.

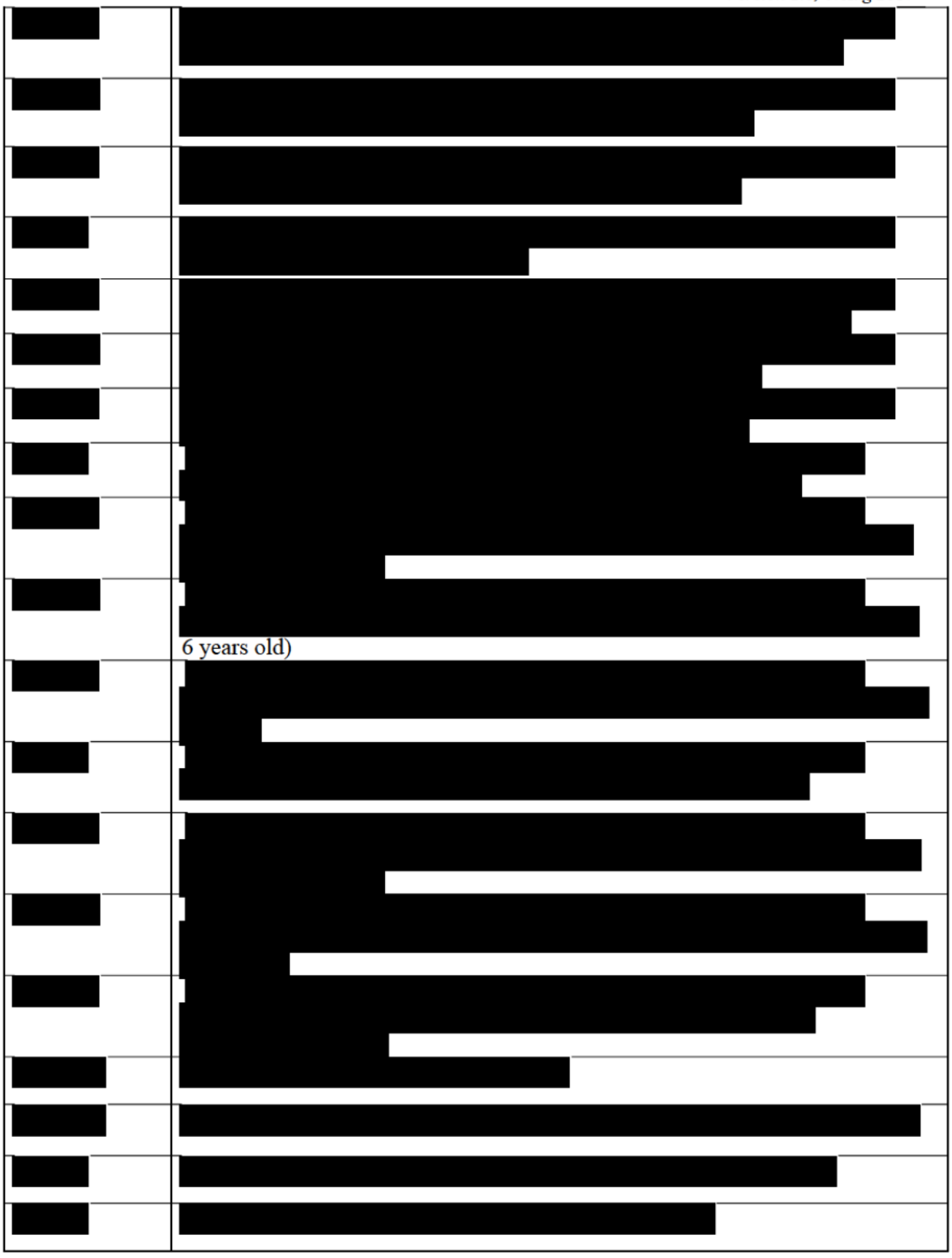
11. TABLES AND LISTINGS CONVENTIONS

Tables and data listings will be created from different SAS programs. A single program may produce multiple tables or multiple data listings from the same dataset (e.g., all clinical chemistry data listings may be generated by a single program).

In general, data listings should include all subjects with data. However, if only subjects who meet a certain condition are listed (e.g., subjects with SAEs) and no subjects meet the condition, the data listing will so indicate.

The sort order for data presented in data listings will be by subject number, unless otherwise requested by Horizon Pharma. Within a subject, data will be listed in chronological order. Whenever possible, formatted values will be displayed (i.e., decoded). Where applicable, calendar date and relative day of evaluations/events will be provided in the data listings.

12. LIST OF STATISTICAL TABLES, LISTINGS, AND FIGURES TO BE PROGRAMMED


6 years old)

[redacted]

completed RP103-03)

14.3.2.2b [redacted]

[redacted]

Population - Patients <= 6 years old)

14.3.5.4c [redacted]

12.3. Figures

Figure Number	Title
1	Mean (+/- SD) Concentrations of WBC Cystine (nmol half Cystine/mg protein) versus Time (Collected Visit) PK/PD Population