CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
Application Number(s)	NDA 203,389 (S-020)
Priority or Standard	Priority
Submit Date(s)	June 29, 2017
Received Date(s)	August 16, 2017
PDUFA Goal Date	December 15, 2017
Division/Office	Division of Gastroenterology and Inborn Errors Products/ODE3/CDER
Reviewer Name	Wen-Yi Gao, M.D., Ph.D.
Review Completion Date	December 1, 2017
Established/Proper Name	Cysteamine Bitartrate
(Proposed) Trade Name	Procysbi Delayed-release Capsules, 25 and 75 mg
Applicant	Horizon Pharma USA, Inc.
Dosage Form(s)	Oral
Applicant Proposed Dosing Regimen(s)	Adjust dose based on white blood cell cysteine concentration
Applicant Proposed Indication(s)/Population(s)	Treatment of nephropathic cystinosis in adult and pediatric patients aged birth and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of nephropathic cystinosis in adult and pediatric patients 1 year of age and older

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Glossary

AC	Advisory committee
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the plasma concentration-time curve
AUC_{inf}	Area under the plasma concentration-time curve from time zero to infinity
AUC_{last}	Area under the plasma concentration-time curve, from time 0 to the time of the last measurable concentration (720 minutes). Same as AUC0-t
BM	Bi-Monthly
BMI	Body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	Body surface area
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Oral clearance
CLss/F	Oral clearance at steady state
Cmax	Maximum observed plasma concentration
Cmin	Minimum observed plasma concentration
CMC	Chemistry, manufacturing, and controls
CPK	Creatine phosphokinase
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CRO	Contract research organization
CSR	Clinical study report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCTD	Electronic common technical document
eCRF	Electronic CRF

EC50	Drug concentration producing 50% of the maximal inhibition
eDiary	Electronic case report form
eGFR	Estimated glomerular filtration rate
Emax	Maximum effect
ESI	Electrospray ionization
E0	Baseline (pre-dose) cystine content
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GM	Geometric mean
G-tube	Gastrostomy tube
HEENT	Head, eyes, ears, nose, and throat
HILC	Hydrophobic interaction liquid chromatography
HPLC	High-pressure liquid chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IR	Immediate release
IRB	Institutional Review Board
ITT	Intent to treat
Ka	First-order absorption rate constant
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
Min	Minutes
mmHg	Millimeters of mercury
MS	Mass spectrometry
NCA	Non-compartmental analysis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OTC	Over the counter
PD	Pharmacodynamic
PICC	Peripherally inserted central catheter

PK	Pharmacokinetics
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PP	Per protocol
PPI	Proton pump inhibitor
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PT	Preferred term
Q6H	Every 6 hours
Q12H	Every 12 hours
Q	Quarterly
REMS	Risk evaluation and mitigation strategy
RP103	Cysteamine Bitartrate Delayed-release Capsules
SAE	Serious adverse event
SD	Standard deviation
SOS	System organ class
t½	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to maximum observed plasma concentration
V/F	Apparent volume of distribution
Vc/F	Apparent volume of distribution of central compartment
WBC	White blood cell

1. Executive Summary

1.1. Product Introduction

Procysbi (cysteamine bitartrate) delayed-release capsules are a cysteine-depleting agent for the treatment of nephrophathic cystinosis. It was approved in 2013 for adult and pediatric patients age 6 years and older. The indication was extended to age 2 years and older in 2015.

In this efficacy supplement, the Applicant proposes (1) revising the label so that the indicated population is patients age 1 year and older and revising other sections of the label to include results of the submitted study in treatment-naïve nephropathic cystinosis patients (Study RP103-08); and (2) to complete the Pediatric Written Request Determination. This review primarily assesses the effectiveness of Procysbi in reduction of white blood cell cystine levels and in improvements of body weight and standing height. A total of 15 pediatric patients age <6 years were enrolled. Fourteen of them completed 12-month treatment, and 10 of the 14 continued to complete 18-month treatment. The results show that the mean cystine level was numerically decreased from 3.1 nmol ½ cystine/mg protein on Day 1 to 0.80 nmol at Month 12 of Procysbi treatment. Responder analysis shows that the proportion of subjects who had low WBC cystine levels (<1.0 nmol ½ cystine/mg protein) increased from 20.0% on Day 1 to 76.9% at Study Exit (Note: There were 10 subjects who completed 18-month study and 3 subjects who completed 12-month study). The chronic renal disease was stabilized as demonstrated by the increase of estimated GFR from 55 mL/min/1.73 m^2 at baseline to 63 mL/min/1.73 m^2 at Study Exit.

The clinical data show that the mean height increased from 2.5 percentile on Day 1 to 50.5 percentile at Study Exit. The mean Z-scores of heights increased from -3.1 (Day 1) to 0.1 (Study Exit). The mean weight increased from 3.4 percentile on Day 1 to 32.8 percentile at Study Exit. The mean Z-scores of weights increased from -3.9 (Day 1) to -1.1 (Study Exit).

Safety assessment of Study RP103-08 (15 Procysbi-treatment naïve patients) shows one death (1/15, 6%) due to gastroenteritis, vomiting, and hypovolemic shock. There were 4 patients (4/15, 26%) who had vomiting defined as serious adverse events (SAEs, non-fatal). The most common adverse events (AEs) were vomiting (8/15, 53%), gastroenteritis (5/15, 33%), and diarrhea (3/15, 20%).

The benefit-risk evaluations are listed as follows:
Benefits:

- Treatment benefit: Nephropathic cystinosis is a life-threatening disease. Young cystinotic patients die of end-stage renal disease due to accumulation of intracellular cystine. Procysbi decreased the cellular cystine levels and stabilized kidney function as measured by the estimated GFR.
- Clinical significance: Percentiles of body weight and standing height increased along with Z-scores improvements during the 12-month of Procysbi treatment.
- Unmet medical need: Nocturnal accumulation of cystine in cystinosis requires strict cystagon dosing regimen every 6 hours (Levtchenko, 2006). A 3-hour delay of the nocturnal cystagon dose (from 6-hour nocturnal interval to 9-hour interval) increases WBC cystine levels by 60% (Levtchenko, 2006). Procysbi delayed release capsules do not require every 6-hour administration, therefore, prevent nocturnal accumulation of cystine in cystinosis.

Risks:
Treatment-emergent vomiting: 26% (4/15) vomiting as SAE, and 53% (8/15) vomiting as non-SAE.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In summary, the Applicant has provided reasonable evidence to support the effectiveness of Procysbi for treating nephropathic cystinosis. From the Clinical Reviewer's perspective, the results of treating nephropathic cystinosis are clinically meaningful. The Clinical Reviewer recommends approval of this efficacy supplement for Procysbi for the treatment of nephropathic cystinosis in treatment-naïve patients age 1 to 6 years old.

Pediatric Written Request and Exclusivity Determination are reviewed under Section 8.7.3. The Applicant fulfilled the Written Request. The clinical reviewer recommends granting Pediatric Exclusivity.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

The Benefit-Risk assessment reveals favorable results for Procysbi treated treatment-naïve nephropathic cystinosis patients age less than 6 years old. Study RP103-08 shows that it decreased the mean cystine concentration of white blood cell from 3.1 (Day 1) to 0.8 nmol ½ cystine/mg protein (Month 12). The proportion of patients who had low WBC cystine (< 1.0 nmol ½ cystine/mg protein) was increased from 20% (Day 1) to 61% (Month 12). The renal function was stabilized as measured by eGFR, a 14% increase at Study Exit (10 patients completed 18-month treatment and 3 patients completed 12-month treatment) from baseline. The mean height of patients increased from 2.5 percentile (Day 1) to 50.5 percentile at Study Exit. This increase correlates with Z-scores increase from -3.1 to 0.1 as determined by the CDC method adjusted for each subject's gender and age. The mean weight was increased from 3.4 percentile (Day 1) to 32.8 percentile (Study Exit), and Z-scores increased from -3.9 to -1.1.

Tolerability study shows 26% (4/15) of patients (age <6 years) experienced vomiting as severe adverse events. Additional 53% (8/15) of patients had vomiting as non-SAE, suggesting that treatment-naïve patients age <6 years are susceptible to Procysbi-induced vomiting than the patients age ≥6 years.

In summary, strict every 6 hours cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystagon-treated cystinosis. Procysbi delayed-release capsules has a dosing regimen of two divided doses (every 12 hours) and thus addresses an unmet medical need. This efficacy supplement supports the favorable benefit-risk assessment of Procysbi in treatment-naïve patients age <6 years.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Nephropathic cystinosis is a rare autosomal recessive lysosomal storage disorder caused by mutations in the CTNS gene that codes for a cystine transporter in the lysosomal membrane. Affected patients store 50 to 100 times the normal amounts of cystine in their cells, and suffer from renal tubular and glomerular disease, growth retardation, eye dysfunction and	Nephropathic cystinosis is a life-threatening disease. Untreated patients will die from end-stage renal disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	other systemic complications. The estimated prevalence is 500 cases in the United States. Approximately 95% of pediatric patients with cystinosis have Fanconi syndrome. According to a report of 205 cystinotic patients from European countries, the median survival time of untreated patients was 8.5 years; the median time for developing end-stage renal disease, defined as uremia requiring renal replacement therapy, was 9.2 years; and the youngest patient dying of renal death was 5.2 years (Gretz, 1982).	
Current Treatment Options	Current FDA-approved treatments: • Procysbi therapy: no information regarding treatment naïve patients until Study RP103-08. • Cystagon therapy: requires strict dose every 6 hours to prevent nocturnal cystine accumulation in cystinosis.	Procysbi may provide better treatment for preventing nocturnal cystine accumulation.
Benefit	Benefits: • Mean cystine concentration of white blood cell decreased from 3.1 (Day 1) to 0.8 nmol ½ cystine/mg protein (Month 12). • Proportion of patients who had low WBC cystine (< 1.0 nmol ½ cystine/mg protein) was increased from 20% (Day 1) to 61% (Month 12). • Renal function at Study Exit was stabilized as measured by eGFR, 14% increase from baseline. • Mean height of patients increased from 2.5 percentile (Day 1) to 50.5 percentile at Study Exit (10 patients completed 18-month treatment and 3 patients completed 12-month treatment). This increase correlates with Z-scores increase from -3.1 to 0.1 as determined by the CDC method adjusted for each subject's gender and age. • Mean weight was increased from 3.4 percentile (Day 1) to 32.8 percentile	Procysbi treatment reduced WBC cystine levels and improved renal function (eGFR) in cystinosis patients. The treatment also improved several growth parameters.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(Study Exit), and Z-scores increased from -3.9 to -1.1.	
Risk and Risk Management	Risks and Risk Management: • 26% (4/15) of patients (age <6 years) experienced vomiting as severe adverse events. 53% (8/15) of patients had vomiting as non-SAE. • Common treatment-emergent adverse events were vomiting, diarrhea, and gastroenteritis. • Vomiting and diarrhea can be managed clinically. REMS (Risk Evaluation and Mitigation Strategy) is not required.	Treatment-naïve patients age <6 years appear more susceptible to Procysbi induced vomiting than the patients age ≥6 years.

1.4. Patient Experience Data

This was a Pediatric Written Request study in cysteamine-treatment naïve patients age <6 years. Patient experience data were not requested by the Written Request on August 19, 2013 (amended on October 6, 2015).

2. Therapeutic Context

2.1. Analysis of Condition

Disease Background

Nephropathic cystinosis is a rare autosomal recessive lysosomal storage disorder caused by mutations in the CTNS gene that codes for a cystine transporter in the lysosomal membrane. Affected patients store 50 to 100 times the normal amounts of cystine in their cells, and suffer from renal tubular and glomerular disease, growth retardation, eye dysfunction and other systemic complications.

The estimated prevalence is 500 cases in the United States. Approximately 95% of pediatric patients with cystinosis have Fanconi syndrome. According to a report of 205 cystinotic patients from European countries, the median survival time of untreated patients was 8.5 years; the median time for developing end-stage renal disease, defined as uremia requiring renal replacement therapy, was 9.2 years; and the youngest patient dying of renal death was 5.2 years (Gretz, 1982).

Diagnosis

The diagnosis is made by measuring the leukocyte cystine content. Polymorphonuclear leukocytes are prepared from heparin-treated blood. In this submission, cystine levels are measured using a validated high-performance liquid chromatography (HPLC) coupled with tandem mass spectrometry method, and the total protein content in WBC lysates are assayed by the bicinchrominic acid method.

2.2. Analysis of Current Treatment Options

Cystagon Treatment

Cystagon (cysteamine bitartrate immediate-release form) was approved for treatment of

nephropathic cystinosis in children and adults in August 1994. The recommended maintenance dose is 1.3 grams/m^2/day in 4 divided doses, every 6 hours.

Cystagon dosing requires strict cysteamine administration to prevent nocturnal cystine accumulation. A study by Levtchenko (Levtchenko, 2006) shows that a 9-hour night pause brings about more than 60% increase of WBC cystine level as compared with every 6-hour dosing group with the same daily dose. Waking-up young pediatric patients every night at 2 am for administration of cystagon brings about a compliance issue.

Procysbi Treatment

Procysbi delayed-release capsules were approved in April 2013 for the treatment of nephropathic cystinosis in adults and children age 6 years and older. The indication was extended to age 2 years in August 2015. Total daily dose is 1.3 gram/m^2/day in two divided doses, every 12 hours.

The assessment of pharmacokinetic parameters in treatment-naïve patients age less than 6 years was not conducted until this submission.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Procysbi was initially approved in the U.S. in 2013 for the treatment of nephropathic cystinosis in adults and pediatric patients age 6 years and older. The indication extended to age 2 years and older in 2015.

3.2. Summary of Presubmission/Submission Regulatory Activity

Development of Procysbi was under IND 103,694:

- The Pre-IND meeting was held on December 11, 2008. The Division agreed that a 505(b)(2) application would be acceptable; also, the Division agreed that white blood cells cystine level (measured in nmol ½ cystine/mg protein) was an acceptable primary efficacy endpoint for the pivotal study (RP103-03).
- The IND was submitted on April 17, 2009 and the first pilot study RP103-01 opened.
- The EOP2 meeting was held on January 28, 2010. The Division recommended that the Applicant submit a Special Protocol Assessment (SPA) for review prior to initiating phase 3 trials.
- The Applicant submitted the first and the second versions of the SPA for Study RP103-

03 on March 3, and May 10, 2010, respectively.

- The Pre-NDA meeting was held on October 25, 2011.
- The original NDA 203389 was submitted on March 30, 2012.
- On August 19, 2013, FDA issued a Pediatric Written Request to conduct an open-label, PK/PD, safety and efficacy study in patients aged birth to <6 years, followed for at least one year of treatment with Procysbi.
- (b) (4)
- (b) (4)
- On July 14, 2014, the Applicant submitted the sNDA supplements (b) (4) S010 for the previous sNDA review.
- On June 29, 2017, the Applicant submitted the third sNDA supplement S020 to include the PK/PD parameters and growth parameters from treatment naïve pediatric patients age <6 years old.

3.3. Foreign Regulatory Actions and Marketing History

The authorization status of Procysbi in foreign markets is summarized in Table 1.

Table 1: Foreign Market Authorization of Procysbi

Country/Region	Brand Name	Indication(s)	Registration Status	Marketing Authorization Holder
Canada	PROCYSBI	Treatment of nephropathic cystinosis	New Drug Submission (NDS 161883) approved June 13, 2017	Horizon Pharma Ireland Limited
European Union/European Economic Area	PROCYSBI	Treatment of proven nephropathic cystinosis	Marketing authorization granted Sep 6, 2013 via the centralised procedure (EMEA/H/C/002465)	Chiesi Orphan B.V.

From Section 1.13.10 Foreign Marketing of NDA 203389 S020, upon request received on 11/2/2017.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI audit was not conducted.

4.2. Product Quality

Product quality assessment was not conducted.

4.3. Clinical Microbiology

Clinical microbiology assessment was not conducted.

4.4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology assessment was not conducted.

4.5. Clinical Pharmacology

The final review of clinical pharmacology was not completed at the time the clinical review was due. Based on preliminary discussions within the review team, the clinical pharmacology reviewer did not identify any issue that affected the overall benefit-risk assessment.

4.5.1 Mechanism of Action

Cysteamine bitartrate is the active component of Procysbi. Cysteamine is an aminothiol that enters lysosomes, and participates in the reaction of thiol-disulfide interchange. The reaction converts cystine into cysteine and cysteine-cysteamine mixed disulfide. Both products can exit the lysosomes.

4.5.2 Pharmacodynamics

On December 11, 2008 at the Pre-IND meeting, the Division agreed that white blood cells cystine level (measured in nmol ½ cystine/mg protein) was an acceptable primary efficacy endpoint for the pivotal study (RP103-03). Thus, PD studies measure the changes of WBC cystine levels in the presence of cysteamine.

In general, the normal range (including individuals who are heterozygous for cystinosis) is <0.2

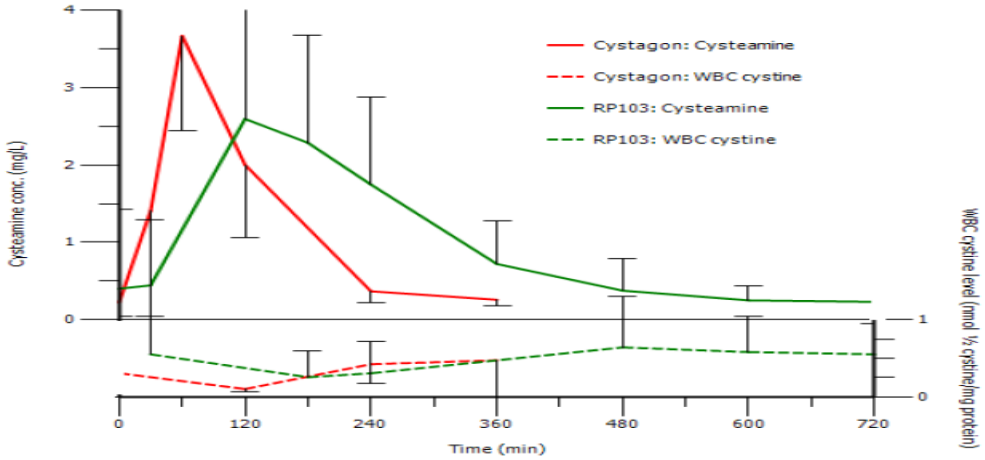
nmol ½ cystine/ mg protein. The therapeutic range is <1 nmol ½ cystine/mg protein. This is defined as the trough levels below the upper limit for heterozygous carriers who are asymptomatic.

4.5.3 Pharmacokinetics

A two-compartment model with first-order absorption and lag time appropriately was used to describe the PK data of Study RP-03 (age ≥6 years). This model shows that at steady state in patients with cystinosis, cysteamine is rapidly cleared from plasma after one dose of Procysbi (Cl/F = 0.03 L min-1 kg-1). Absorption lag time for Procysbi is Tlag = 86 min vs. 28 min for Cystagon.

The average pharmacokinetic and pharmacodynamic profile of plasma cysteamine concentration vs. WBC cystine is compared in the following figure.

Figure 1: WBC Cystine versus Cysteamine: Two Compartment Population PK Model; Inhibitory Tmax Pharmacodynamics in Patients Age ≥6 years



From Study RP103-03 Report, Page 60.

4.6. Devices and Companion Diagnostic Issues

There was no companion device or diagnostic information submitted.

4.7. Consumer Study Reviews

There was no consumer study information submitted.

5. Sources of Clinical Data and Review Strategy

Study RP103-08 has 4 types of clinical data to be reviewed: (1) Pharmacodynamic data: WBC cystine level measurements at each clinical visit, (2) Growth parameters: Standing height, body weight, body mass index, and BSA at each clinical visit, (3) Pharmacokinetic data: AUClast, AUCinf, Cmax, Cmin, t½, Tmax, λz, CLss/F and V/F, and (4) Safety data: Treatment emergent adverse events, serious adverse events (SAEs), the most common AEs, clinical laboratory test (hematology, chemistry, and urinalysis), physical examinations, vital signs, and 12-lead ECGs. Safety data were collected at each visit. This review focuses on the evaluation of WBC cystine level measurements, the growth parameters changes, and the safety data.

Assessment of the pharmacokinetic data defers to the Clinical Pharmacology Reviewer's opinion.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study RP103-08

6.1.1. Study Design

Overview and Objective

Study Title: "An Open-Label, Safety and Effectiveness Study of Cysteamine Bitartrate, Delayed-release Capsules (RP103) in Cysteamine Treatment Naïve Patients with Cystinosis"

The primary objective of this trial was to assess the safety and effectiveness of long-term, repeat dosing of Procysbi on white blood cell cysteine levels in subjects who were cysteamine treatment naive.

The secondary objectives:

- To assess steady-state cysteamine pharmacokinetics (PK)/pharmacodynamics (PD) in children 2 years to 6 years

Trial Design

This was a long-term, open-label study of the safety, tolerability, and effectiveness of Procysbi in patients with cystinosis who were naïve to any form of cysteamine treatment. This study was conducted to evaluate safety and efficacy in children <6 years of age to meet the Written Request.

Procysbi starting dose was based on the subject's age, weight, and body surface area (BSA); and the dose was gradually escalated (10% steps, every 2 weeks) until the subject's WBC cystine level was <1 nmol ½ cystine/mg protein. A subject was considered to have completed the Titration period and entered the Maintenance period when dose adjustments ceased.

Procysbi was administered orally or via gastrostomy tube (G-tube). The daily dose was divided into 2 doses, given every 12 hours. Procysbi treatment continued for at least 12 months. Withdrawn consent prior to completing their last visit was allowed.

Study visits consisted of bi-monthly visits for 6 consecutive visits followed by 3 or more quarterly visits:

- Screening Visit: occurred up to 7 days prior to enrollment, or on Day 1.
- Day 1 Visit: the day of enrollment and start of Procysbi dosing.
- Bi-Monthly Visits: began within 2 weeks (±3 days) after the Day 1 Visit. Each subject completed 6 bi-monthly visits before proceeding to a quarterly visit schedule.
- Quarterly Visits: took place by the first week of the first month of the calendar quarter (±7 days). Note that the first Quarterly Visit was scheduled slightly more or slightly less than 3 months after the sixth bi-monthly visit in order to eventually harmonize all subjects' bioanalysis schedule (i.e., PK and PD analysis by the central laboratory to occur mid-January, mid-April, mid-July, and mid-October). Each subject completed at least 3 quarterly visits.
- Study Exit Visit: took place within 7 (±2 days) from the last completed study visit or from the date of decision to terminate.

Study evaluations included WBC cystine levels 30 minutes post the Procysbi morning dose at each study visit, standing height and standing weight at each visit, steady-state plasma concentration profiles of cysteamine and plasma PK parameters, and safety assessments (incidence of treatment-emergent adverse events [TEAEs] and treatment-emergent serious adverse events [SAEs], clinical laboratory tests [hematology, chemistry, and urinalysis], physical examinations, vital signs, and 12-lead electrocardiograms [ECGs]).

Table: 2: Schedule of assessments.

PROCEDURE	Screening	Day 1	Bi-Monthly (every 2 week) Visits[a]	Quarterly (every 3 month) Visits[b]	Study Exit[c]
Visit Number	*1*	*2*	*3–8*	*9, 10, 11, etc.*	*Final*
Allowable Visit Window	*up to 7 days*	*None*	*±3 days*	*±7 days*	*see footnote[c]*
Informed Consent	X				
Assess/Confirm Eligibility	X	X			
Enrollment		X			
Demographic Data	X				
Medical & Medication Histories	X				
Monitoring of Adverse Events	X[d]	X	X	X	X
Review of Concomitant Medications	X	X	X	X	X
Vital Signs	X	X	X	X	X
Body Height and Weight	X	X	X	X	X
BMI / BSA Calculations	X	X	X	X	X
ECG	X		X	X	X
Physical Examination	X		X	X	X
Clinical Laboratory Tests[e]	X		X[f]	X	X
Serum Pregnancy Test (if applicable)	X	X	X	X	X
Medication Diary Training	X				
Medication Diary Review / Sign		X	X	X	X
Medication Diary Re-dispense		X	X	X	
RP103 Administration		X	X	X	X
RP103 Dose Adjustment			X	X	
PK Sample Collection[g]		X	X	X	X
PD Sample Collection[h]		X	X	X	X

BMI = body mass index; BSA = body surface area; CRF = case report form; ECG = electrocardiogram; PD = pharmacodynamic; PK = pharmacokinetic; WBC = white blood cell

Note: A subject was considered to have completed the Titration period and entered the Maintenance period when dose adjustments ceased.

[a] Bi-Monthly Visits began 2 weeks (±3 days) after the Day 1 Visit. Each subject completed 6 Bi-Monthly Visits before proceeding to a quarterly visit schedule.

[b] Each subject completed at least 3 Quarterly Visits.

[c] Study Exit Visit was performed 7 ±2 days after the subject's last study drug dose or the decision to terminate.

[d] Adverse event monitoring began upon Informed Consent signing.

[e] Clinical laboratory tests included chemistry, hematology, and urinalysis tests, as specified in Section 9.5.1.3.1.

[f] Clinical laboratory tests were performed at every other Bi-Monthly Visit (i.e., at Month 1, Month 2, and Month 3).

[g] PK (plasma cysteamine) samples were collected as follows:

Day 1 and Bi-Monthly Visits: 30 minutes after the morning RP103 dose.

Quarterly and Study Exit visits: a target of 30 minutes after the morning RP103 dose (permissible between 20-35 minutes after the morning dose for subjects enrolled under Protocol Amendment 1 or later).

Quarterly Visit #1 (Month 6): 30 minutes after the morning RP103 dose (prior to Protocol Amendment 1); or 9 time points – 0 (pre-dose) and 30 minutes, 2, 3, 4, 6, 8, 10, and 12 hours after the morning RP103 dose for subjects enrolled under Protocol Amendment 1 or later.

[h] PD (WBC cystine) samples were collected as follows:

Day 1 and Bi-Monthly Visits: 30 minutes after the morning RP103 dose.

Quarterly and Study Exit visits: a target of 30 minutes after the morning RP103 dose (permissible between 20-35 minutes after the morning dose for subjects enrolled under Protocol Amendment 1 or later).

Quarterly Visit #1 (Month 6): 30 minutes after the morning RP103 dose (prior to Protocol Amendment 1); or 3 time points – 0 (pre-dose) and 2 sampling times that are time-matched with PK sample collection (i.e., 3 and 8 hours, 3 and 10 hours, 3 and 12 hours, 4 and 8 hours, 4 and 10 hours, or 4 and 12 hours) after the morning RP103 dose for subjects enrolled under Protocol Amendment 1 or later. The 2 post-dose time points for each subject were determined by randomization via the electronic CRF database.

Inclusion Criteria (RP103-08)

1. Male or female with a documented diagnosis of cystinosis.
2. No clinically significant change in liver function tests, i.e., 1.5 times upper limit of normal (ULN) for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and/or 1.5 times ULN for total bilirubin, within 6 months prior to Screening.
3. No clinically significant change in renal function, i.e., eGFR within 6 months prior to Screening.
4. Estimated GFR >20 mL/min/1.73 m2 (using the equation from Schwartz 2009).
5. Female subjects who were sexually active and of childbearing potential, i.e., not surgically sterile (tubal ligation, bilateral oophorectomy, or hysterectomy) or at least 2

years naturally postmenopausal, must have agreed to use an acceptable form of contraception from Screening through completion of the study. Acceptable forms of contraception included hormonal contraceptives (oral, implant, transdermal patch, or injection) at a stable dose for at least 3 months prior to Screening, barrier (spermicidal condom or diaphragm with spermicide), intrauterine device (IUD), or a partner who had been vasectomized for at least 6 months. (NB: It was not anticipated that subjects younger than 6 years would be of childbearing potential. Childbearing potential was defined as a female subject who had reached menarche)

6. Subject or their parent or guardian must have provided written informed consent and assent (where applicable) prior to participation in the study.
7. Had not taken any form of cysteamine bitartrate in the past.

Exclusion Criteria (Study RP103-08)

1. Subjects who had a history of the following conditions or any other health issues that made it, in the opinion of the Investigator, unsafe for study participation:
   - Inflammatory bowel disease if currently active, or prior resection of small intestine;
   - Heart disease (e.g., myocardial infarction, heart failure, unstable arrhythmias, or poorly controlled hypertension) within 90 days prior to Screening;
   - Active bleeding disorder 90 days prior to Screening;
   - History of malignant disease within 2 years prior to Screening.
2. Hemoglobin level <10 g/dL at Screening or, in the opinion of the Investigator, a hemoglobin level that would have made it unsafe for study participation.
3. Known hypersensitivity to penicillamine.
4. Female subjects who were nursing, planning a pregnancy, or were known or suspected to be pregnant.
5. Subjects who, in the opinion of the Investigator, were not able or willing to comply with study requirements.
6. Had received a kidney transplant or was currently on dialysis.
7. Was 6 years of age or older at the time of the Screening Visit (for enrollment under Protocol Amendment 1 or later, see Section 9.8.1).

Study Endpoints

1. Pharmacodynamic (PD) Endpoint

The PD endpoint was white blood cell (WBC) cysteine levels 30 minutes post Procysbi oral dose at each study visit. This time point corresponds to the steady-state cysteamine-trough concentration.

2. Growth Parameters

The growth parameters were the following:

- Standing height

- Standing weight
- Body mass index (BMI)
- Body surface area (BSA)

3. Pharmacokinetic Endpoints

The steady-state plasma concentration profiles of cysteamine were determined for each subject, and the following plasma PK parameters were estimated using non-compartmental analysis.

- AUC_{last} Area under the plasma concentration-time curve from time 0 to time of the last measurable concentration (720 minutes), calculated by the linear trapezoidal linear interpolation method. (Same as AUC_{0-t})
- AUC_{inf} Area under the plasma concentration-time curve from time 0 extrapolated to infinity, calculated as the sum of the AUC_{0-t} and the ratio of the last measurable plasma concentration to λz.
- C_{max} Maximum observed plasma concentration.
- C_{min} Minimum observed plasma concentration.
- t½ Apparent terminal elimination half-life, calculated as 0.693/ λz.
- T_{max} Time of the maximum observed plasma concentration. If the maximum value occurred at more than 1 time point, Tmax was defined as the first time point with this value.
- λz Apparent terminal elimination rate constant, estimated by linear regression on the terminal phase of the semi-logarithmic plasma concentration-versus-time curve.
- CLss/F The apparent total body (oral) clearance from plasma, calculated as Dose/AUC_{0-tau} (tau was the dosing interval for steady-state data). Since tau was 720 minutes in this study, AUC_{0-tau} is the same as AUC_{last}.
- V/F The apparent volume of distribution based on the terminal phase, calculated by Dose/(AUC_{0-tau} × λz). Since tau was 720 minutes in this study, AUC0-tau was the same as AUC_{last}.

Medical Officer Comment: Assessment of PK data is deferred to the Clinical Pharmacology reviewer.

4. Safety Endpoints

The safety endpoints were the following:

- Incidence of TEAEs and treatment-emergent SAEs
- Clinical laboratory tests
- Physical examinations
- Vital signs
- 12-lead ECGs

Statistical Analysis Plan

The analysis populations used in this study are summarized in Table 3. All 17 enrolled subjects were included in all 3 populations Safety, PD, and PK populations.

Table 3: Analysis Populations (All subjects)

Population		Number (%) of Subjects
Safety	All subjects who received at least 1 dose of RP103. The Safety Population was used for the analysis of demographic/baseline characteristics, medical history, study drug exposure, and safety endpoints.	17 (100)
PD	All subjects who received at least 1 dose of RP103 and who had at least 1 WBC cystine level recorded. The PD Population was used for analysis of demographic/baseline characteristics, WBC cystine level data, and growth parameters.	17 (100)
PK	All subjects who received at least 1 dose of RP103 and who had available PK data. The PK Population was used for the analysis of demographic/baseline characteristics and PK parameters.	17 (100)

Source: Table 14.1.1.
PD = pharmacodynamic; PK = pharmacokinetic; WBC = white blood cell.

From Study Report of RP103-08, Page 66.

Note: Of the 17 enrolled subjects, the numbers included in each age subgroup were as follows:

- >6 years old: 2 subjects;
- <6 years old: 15 subjects;
- ≥2 years old and <6 years old: 8 subjects
- <2 years old: 7 subjects

Protocol Amendments

There were 2 amendments. There was no change of study endpoint and methods of assessing the endpoint. The Applicant provided the rationale for the amendments. All the changes were reviewed. These modifications did not change the integrity of the trial or reviewer's interpretation of the results.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that Study RP103-08 submitted to this NDA was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP). The study was conducted under IND 103694.

Financial Disclosure

The Applicant has adequately disclosed financial interests or arrangements with the clinical investigators (see Appendix 13.2). The sponsor stated that none of the clinical investigators received significant payments as defined in 21 CFR 54.2(a), (b), and (f).

Medical Officer Comments:
The Applicant has reasonably disclosed financial arrangements with clinical investigators in this application. The submitted financial disclosures do not raise concerns which would possibly jeopardize the integrity of the data.

Patient Disposition

A total of 17 subjects were enrolled; of these, 15 subjects were <6 years of age. Among subjects <6 years of age, the mean (± SD) number of days of study drug exposure was 511.7 ±158.11 (median 575.0 days; range 17-611 days). Fourteen of the subjects completed the study (i.e., at least 12 months of treatment): 4 subjects completed at least 12 months of treatment, and 10 subjects completed at least 18 months of treatment. One subject withdrew early (death on Day 18). The event leading to death was gastroenteritis. The investigator stated that the death was likely related to the underlying cystinosis and not related to the study drug.

Protocol Violations/Deviations

No subject was withdrawn from the study or excluded from an analysis population because of a protocol deviation. A total of 6 subjects did not satisfy all the inclusion/exclusion criteria (Table 4). These subjects had hemoglobin <10 g/dL (5 subjects) or unknown hemoglobin (1 subject) and therefore were to be excluded per exclusion criterion #2 (subjects with hemoglobin level of <10 g/dL at Screening or other unsafe level in the Investigator's opinion). Enrollment of all 6 subjects was granted by the Sponsor. The other major protocol deviations (in the opinion of the Investigator) are summarized in Table 4.

There was an error in processing 16 of the samples for PD analyses (approximately 7% of all PD samples collected). An incorrect diluent was used to suspend pelleted WBCs. The samples were recentrifuged, and the solution was analyzed. The remaining pellet was re-dissolved in the correct diluent and analyzed according to correct processes. Because of this error, it was not possible to analyze duplicate samples for the 16 samples. However, the Applicant stated that since the samples were analyzed using the correct procedure, this deviation did not affect the integrity of the study and was considered a minor deviation. Documentation of the method deviation, the investigation, and the results is included in the study master file. Minor deviations included missed assessments, visits or assessments performed outside of the

protocol-specified window, missed doses, noncompliance (e.g., milk ingested too close to study drug administration; study drug dosing not recorded), and study drug bottles not returned. These were isolated occurrences for the individual subjects and were not expected to influence the outcome of the study.

Table 4: Major Protocol Deviations (All Subjects)

Subject	Deviation	Visit	Category
01-009	Subject did not meet inclusion criterion of hemoglobin of 10 g/dL or greater. Investigator believed that the benefits of the study outweighed the risk. Medical Monitor notified. Exception approved.	Screening	Eligibility
01-010	Subject had a hemoglobin <10 g/dL, which is 1 of the criteria for study exclusion. Investigator felt the benefit of enrolling in the study outweighed any risk.	Screening	Eligibility

(Continued)

Subject	Deviation	Visit	Category
01-012	The ICF was not signed prior to the first study required procedure at Screening.	Day 1	Outside protocol window
21-002	Screening hemoglobin = 9.8 g/dL. However, <10 g/dL was an exclusion criterion. Investigator assessed this result was related to cystinosis, and that the subject had no other cause for anemia. Exception approved.	Screening	Eligibility
21-003	Subject received only 1 dose of expired study drug because parents didn´t come to the site to get new medication.[1] The subject had no AE or SAE associated with the use of expired drug.	Between study visits	Study drug dosing
21-004	Subject took expired study drug during a 3-day period.[1] No AEs or SAEs were associated with the use of expired study drug.	Between study visits	Other (expired study drug intake)
	The study drug intake hour was not recorded on the medical chart – it was not possible to know if PK was collected 30 minutes after the morning dose intake.	Month 9	Other (visit procedure)
21-005	Subject took expired study drug during a 3-day period.[1] No AEs or SAEs were associated with the use of expired study drug.	Between study visits	Other (expired study drug intake)
	The study drug intake hour was not recorded on the medical chart – it was not possible to know if PK was collected 30 minutes after the morning dose intake.	Month 9	Other (visit procedure)
21-006	Screening hemoglobin = 9.7 g/dL. However, <10 is an exclusion criterion. Investigator assessed that this result is related to cystinosis, and that the subject has no other cause for anemia. Exception approved.	Screening	Eligibility
	Subject didn´t attend the visit and did not draw new bottles of medication, so he didn´t take the study medication for a week.	Week 10	Study drug dosing
	Parents were not able to bring subject to study visit during the visit window.	Week 10	Noncompliance
	Subject missed 20 doses of 75 mg pills between 08JUL2015 to 05AUG2015. Subject was 70% compliant with study 75 mg study drug during this period.	Week 12	Noncompliance
	Subject study drug dose was 100 mg twice a day. Between 08JUL2015 to 05AUG2015 just the 25 mg pills were taken and it was not possible to calculate the compliance as the bottle was empty (should have returned 4 pills).	Week 12	Noncompliance
	Subject was not compliant with study medication during Month 3 BM2 and Q1 visits as per diary records. Study drug accountability could not be performed because bottles were not returned to site.	Month 6	Noncompliance
	Study drug not returned: it was not possible to calculate the compliance between Q1 and Q2 visits from the 25 mg capsules because 1 bottle was not returned back on the date of Q2 Visit.	Month 9	Noncompliance
21-007	Screening hematology sample clotted. Investigator requested approval to use local labs to verify eligibility (hemoglobin). Exception approved by the Sponsor's Medical Monitor.	Screening	Eligibility

(Continued)

Subject	Deviation	Visit	Category
	Wrong study drug administration procedure was followed: the capsule beads were crushed prior to intake.	Day 1	Study drug dosing
21-008	Study drug not returned: it was not possible to calculate the compliance during Month 2 BM 2 and Q1 visits because subject did not bring 1 bottle dispensed on Month 2 BM 2 on the Q1 visit.	Month 6	Noncompliance
21-010	Between visit Month 2 BM 2 and Q1 visits, subject should have returned 24 capsules of 25 mg and returned 129 capsules.	Month 6	Noncompliance
21-011	Subject presented hemoglobin 8.4 g/dL. However, Sponsor approved this protocol exception.	Screening	Eligibility

Source: Listing 16.2.1.2 and Listing 16.2.2.1.2.
AE = adverse event; BM = Bi-Monthly; ICF = Informed Consent Form; PK = pharmacokinetic; Q = Quarterly; SAE = serious adverse event.
Note: Major deviations, as determined by the Investigator.
Note: All of the subjects with major deviations were <6 years old.
[1] Subject 21-003 took 1 dose of study drug 1 day after the expiration date. Subjects 21-004 and 21-005 took twice daily doses for a 3-day period (days 1, 2, and 3 after the study drug expiration date).

From Study RP103-08 Report, Pages 63-65.

Medical Officer Comments:

● Because some patients did not have WBC cystine samples collected at each visit or results were not reportable due to laboratory errors, the numbers of subjects <6 years of age with available WBC cystine data varied across the time points analyzed.
● In patients with missing samples, dose escalation was continued if the patient's last concentration was > 1.
● PROCYSBI dose adjustment was allowed throughout the study based on subject-specific factors (e.g., level of health fragility, growth rate, compliance, tolerability, availability of WBC cystine level result) and variability of response to PROCYSBI.
● Among the 14 subjects <6 years of age who completed the study, 13 of the 14 subjects achieved their highest total daily dosage of PROCYSBI following the 9-month visit (9-month visit for 8 subjects, 12-month visit for 4 subjects, and 18-month visit for 1 subject). These results suggest that treatment-naïve subjects <6 years of age required dose titration over a period of at least 9 months to achieve the PROCYSBI dosage needed to attain their therapeutic target WBC cystine level.

I agree with the investigator that the deviations had no major impact on the overall study results.

Demographic Characteristics

Demographics and baseline characteristics are summarized in Table 5. Among all 17 subjects, the mean age was 3.8 years, with a range of 1.0 to 22.2 years. Ten subjects were male. Thirteen subjects were White and 4 subjects were Black. Mean weight was 13.9 kg, and mean

BMI was 15.5. Among the 15 subjects who were <6 years old, the mean age was 2.2 years, with the range of 1.0 to 4.5 years. Eight subjects were male. Eleven subjects were White and 4 were Black. Mean weight was 9.0, and mean BMI was 14.9.

Table 5: Demographic and Baseline Characteristics (Safety Population and Subjects Age <6 Years)

Characteristic	Subjects Age <6 Years (N=15)	All Subjects (N=17)
Age (years)[1]		
N	15	17
Mean (SD)	2.22 (0.985)	3.80 (5.116)
Median	2.28	2.33
Min, Max	1.04, 4.53	1.04, 22.26
Age (months)[1]		
N	15	17
Mean (SD)	26.70 (11.816)	45.64 (61.396)
Median	27.40	27.99
Min, Max	12.48, 54.31	12.48, 267.10

(Continued)

Characteristic	Subjects Age <6 Years (N=15)	All Subjects (N=17)
Age Subgroups, n (%)[1]		
N	15	17
<6 years	15 (100.0)	15 (88.2)
<2 years	7 (46.7)	7 (41.2)
≥2 years	8 (53.3)	10 (58.8)
Gender, n (%)		
Male	8 (53.3)	10 (58.8)
Female	7 (46.7)	7 (41.2)
Race, n (%)		
American Indian or Alaska Native	0	0
Asian	0	0
Black	4 (26.7)	4 (23.5)
Native Hawaiian or Other Pacific Islander	0	0
White	11 (73.3)	13 (76.5)
Other	0	0
Ethnicity, n (%)		
Hispanic or Latino	11 (73.3)	11 (64.7)
Not Hispanic or Latino	4 (26.7)	6 (35.3)
Weight (kg)		
N	15	17
Mean (SD)	9.01 (2.015)	13.91 (17.561)
Median	9.30	9.40
Min, Max	5.80, 13.20	5.80, 80.80
Height (cm)		
N	15	17
Mean (SD)	77.12 (7.505)	85.54 (27.704)
Median	79.30	80.50
Min, Max	62.30, 86.10	62.30, 183.70

(Continued)

Characteristic	Subjects Age <6 Years (N=15)	All Subjects (N=17)
BMI (kg/m^2)		
N	15	17
Mean (SD)	14.98 (1.258)	15.56 (2.470)
Median	14.84	14.94
Min, Max	13.39, 17.93	13.39, 23.94
BSA (m^2)		
N	15	17
Mean (SD)	0.44 (0.070)	0.56 (0.395)
Median	0.45	0.45
Min, Max	0.32, 0.57	0.32, 2.03

Source: Table 14.1.2.1 and Table 14.1.2.1.3.
BMI = body mass index; BSA = body surface area; Max = maximum; Min= minimum; SD = standard deviation.
[1] Age = (date of first dose – date of birth)/365.25.

From Study RP103-08 Report, Pages 67-69.

Relevant Medical History

Medical history is summarized in Table 6. All 17 subjects had a history of cystinosis. In addition, the most frequently reported (≥10% subjects) medical history findings were hypothyroidism (6 subjects, 35.3%), Fanconi syndrome (5 subjects, 29.4%), failure to thrive (3 subjects, 17.6%), growth failure (2 subjects, 11.8%), and nausea/vomiting (2 subjects, 11.8%).

Table 6: Medical History (All subjects)

Body System Verbatim Term	All Subjects (N=17) n (%)
Subjects with any reported event	17 (100)
Renal	17 (100)
Cystinosis	12 (70.6)
Fanconi Syndrome	5 (29.4)
Azotemia	1 (5.9)
Chronic Kidney Disease	1 (5.9)
Chronic Kidney Disease, Stage II	1 (5.9)
Kidney Transplant[1]	1 (5.9)
Proteinuria	1 (5.9)
Renal Failure	1 (5.9)
Vitamin D Deficiency	1 (5.9)
Endocrine	8 (47.1)
Cystinosis	5 (29.4)
Hypothyroidism	4 (23.5)
Failure to Thrive	3 (17.6)
Growth Failure	2 (11.8)
Hypothyroid	2 (11.8)
Hyperphosphatemia	1 (5.9)
Hypocalcemia	1 (5.9)
Gastrointestinal/Abdomen	4 (23.5)
Nausea/Vomiting	2 (11.8)
Gastroschisis	1 (5.9)
Low GI Motility	1 (5.9)
Vomiting	1 (5.9)
Cardiovascular	1 (5.9)
Hypertension	1 (5.9)
Dermatological	1 (5.9)
Diaper Rash	1 (5.9)
Genitourinary	1 (5.9)
Polyuria	1 (5.9)

(Continued)

Body System Verbatim Term	All Subjects (N=17) n (%)
HEENT	1 (5.9)
Hyperopia	1 (5.9)
Myopia	1 (5.9)
Hematologic	1 (5.9)
Anemia	1 (5.9)
Musculoskeletal	1 (5.9)
Rickets	1 (5.9)

Source: Table 14.1.3 and Listing 16.2.4.1.
GI = gastrointestinal; HEENT = head, eyes, ears, nose, and throat.
Note: If a subject had more than 1 medical history event in a given body system, that subject is counted once for the body system. If a subject had more than 1 event with a given verbatim term, that subject is counted only once for that verbatim term.
[1] This subject was enrolled prior to Protocol Amendment 1. Subjects who had a kidney transplant were excluded from study enrollment under Protocol Amendment 1 and later.

From Study Report of RP103-08, Page70.

Prior and Concomitant Medication

Prior and concomitant medications were coded using WHO Drug March 2012 and tabulated by Level 4 ATC (anatomical therapeutic class) (chemical subgroup) and PT.

Prior medications are those started prior to the first dose of study drug. A total of 12 subjects (70.6%) reported using at least 1 prior medication. The medication classes most frequently used (≥20% of subjects) were Vitamin D and analogs (10 subjects, 58.8%), Potassium (7 subjects, 41.2%), and Thyroid Hormones (4 subjects, 23.5%). The most frequently used individual prior medications were calcitriol (7 subjects, 41.2%); potassium chloride (6 subjects, 35.3%); and colecalciferol, phosphorus, sodium bicarbonate, and levothyroxine (4 subjects, 23.5% each).

Concomitant medications (those started or continued after the first dose of study drug) used by at least 10% of subjects in the Safety Population are summarized in Table 7. The medication classes most frequently used (≥20% of subjects) were Vitamin D and analogs. The most frequently used individual concomitant medications were potassium chloride, phosphorus, calcitriol, and sodium bicarbonate (>70% of subjects each); ferrous sulfate, ergocalciferol, omeprazole, ranitidine, and mercaptamine (>40% of subjects each); and sodium chloride (electrolyte solution), levothyroxine, colecalciferol, potassium citrate, magnesium sulfate, paracetamol, calcium carbonate, erythropoietin, sodium chloride (nasal preparation), ondansetron, and osmotan (>20% of subjects each).

Table 7: Concomitant Medications Used by ≥10% of Subjects (Safety Population)

Chemical Subgroup Preferred Term[1]	All Subjects (N=17) n (%)
At Least 1 Concomitant Medication	17 (100)
Vitamin D and Analogues	15 (88.2)
Calcitriol	12 (70.6)
Ergocalciferol	8 (47.1)
Colecalciferol	5 (29.4)
Potassium	14 (82.4)
Potassium Chloride	13 (76.5)
Potassium Citrate	5 (29.4)
Various Alimentary Tract and Metabolism Products	13 (76.5)
Phosphorus	13 (76.5)
Sodium Bicarbonate	12 (70.6)
Iron Bivalent, Oral Preparations	9 (52.9)
Ferrous Sulfate	9 (52.9)
Electrolyte Solutions	8 (47.1)
Sodium Chloride	6 (35.3)
Calcium Gluconate	2 (11.8)
Sodium Bicarbonate	2 (11.8)
H2-Receptor Antagonists	8 (47.1)
Ranitidine	7 (41.2)
Ranitidine Hydrochloride	2 (11.8)
Proton Pump Inhibitors	8 (47.1)
Omeprazole	8 (47.1)
Magnesium	7 (41.2)
Magnesium Sulfate	5 (29.4)
Magnesium	2 (11.8)
Other Antiinfectives	7 (41.2)
Mercaptamine	7 (41.2)

(Continued)

Chemical Subgroup Preferred Term[1]	All Subjects (N=17) n (%)
Thyroid Hormones	7 (41.2)
Levothyroxine	6 (35.3)
Amino Acids and Derivatives	5 (29.4)
Levocarnitine	3 (17.6)
Anilides	5 (29.4)
Paracetamol	5 (29.4)
Calcium	5 (29.4)
Calcium Carbonate	5 (29.4)
Other Antianemic Preparations	4 (23.5)
Erythropoietin	4 (23.5)
Other Mineral Products	4 (23.5)
Phos-NaK	3 (17.6)
Other Nasal Preparations	4 (23.5)
Sodium Chloride	4 (23.5)
Propulsives	4 (23.5)
Bromopride	2 (11.8)
Domperidone	2 (11.8)
Serotonin (5HT3) Antagonists	4 (23.5)
Ondansetron	4 (23.5)
Solutions Affecting the Electrolyte Balance	4 (23.5)
Osmotan	4 (23.5)
EI-4	2 (11.8)
Other Combinations of Nutrients	3 (17.6)
Other Combinations of Nutrients	3 (17.6)
Other Urologicals	3 (17.6)
Mist. Pot. Cit.	2 (11.8)
Shohl's	2 (11.8)
Penicillins with Extended Spectrum	3 (17.6)
Amoxicillin	3 (17.6)
Pyrazolones	3 (17.6)
Metamizole Sodium	3 (17.6)
Acetic Acid Derivatives and Related Substances	2 (11.8)
Indometacin	2 (11.8)

(Continued)

Chemical Subgroup Preferred Term[1]	All Subjects (N=17) n (%)
Other Irrigating Solutions	2 (11.8)
Glucose	2 (11.8)
Selective Beta-2-Adrenoreceptor Agonists	2 (11.8)
Salbutamol Sulfate	2 (11.8)
Somatropin and Somatropin Agonists	2 (11.8)
Somatropin	2 (11.8)

Source: Table 14.4.5.
Phos-NaK = potassium phosphate/sodium phosphate; PT = preferred term.
Note: If a subject took more than 1 medication of a given subgroup or PT, that subject is counted once for that subgroup or PT.
[1] Medications coded using World Health Organization Drug Dictionary March 2012.

From Study Report of RP103-08, Page72.

Efficacy Results – Primary Endpoint

The pre-specified primary efficacy endpoint for RP103-08 is WBC cystine level. It is an established pharmacodynamic marker of intracellular cystine depletion that has been shown to correlate with long-term, meaningful clinical outcomes in patients with nephropathic cystinosis (Kleta, 2004; Nesterova, 2015).

(1) Pharmacodynamic findings

The PD findings in the 15 subjects age <6 years are summarized as follows:

- There was a numerical decrease in mean (± SD) WBC cysteine concentration during the Procysbi treatment period, from 3.2 ±2.9 to 0.8 ±0.6 nmol ½ cysteine/mg protein at Day 1 and the last day of the 12-month study.

Table 8: Summary of WBC Cystine at baseline, 6 moths, and 12 months visits (Age <6 Years)

Visit		WBC cystine level
		nmol ½ cystine/mg protein
Day 1	N	15
	Mean (SD)	3.17 (2.95)
	Median	1.78
	Min, Max	0.42, 10.88
Month 3	N	13
	Mean (SD)	1.18 (1.31)
	Median	0.92
	Min, Max	0.09, 5.02
Month 9	N	6
	Mean (SD)	2.01 (1.90)
	Median	1.41

	Min, Max	0.06, 5.13
Month 12	N	13
	Mean (SD)	0.80 (0.59)
	Median	0.63
	Min, Max	0.09, 2.35
Study Exit	N	13
	Mean (SD)	0.81 (0.76)
	Median	0.49
	Min, Max	0.25, 2.94

From Study Report RP103-08, Page 75. Study Exit included 10 subjects who completed 18 months study and 3 subjects who completed 12 months study.

The responder analysis of subjects who reached <1.0 nmol ½ cysteine/mg protein shows that at Day 1, the percentage of subjects was 3/15 (20.0%). It was progressively increased from 6/15 (40.0%) at Week 2, 8/13 (61.5%) at Week 12, 6/9 (66.7%) at Month 18, and 10/13 (76.9%) at Study Exit. At Study Exit, there were 10 subjects who completed 18 months study and 3 subjects who completed 12 months study.

Table 9: Percentage of Subjects Who Reached <1.0 nmol ½ cysteine/mg protein (Subjects Age <6 Years)

Visit	Number of Patients	**Percentage of Responder**
Day 1	N=15	**3/15 (20.0%)**
Week 2	N=15	**6/15 (40.0%)**
Week 12	N=13	**8/13 (61.5%)**
Study Exit	N=13	**10/13 (76.9%)**

Note: Study Exit included 10 subjects who completed 18 months study and 3 subjects who completed 12 months study.

Medical Officer Comments:
WBC cystine levels are used to monitor disease development and to follow cysteamine treatment. It is a common clinical practice that the WBC cystine levels with cysteamine treatment should be below the upper limit of heterozygous carriers who are asymptomatic (Gahl, 2002). The heterozygous carriers have WBC cystine levels range from 0.14 to 0.57, and the recognized successful treatment level is below 1 nmol ½ cystine/mg protein (Wilmer, 2011). The normal range is <0.2.

In Study RP103-08, there were 4 patients age less than 6 years, who had WBC cystine levels <1 on Day 1: i.e. Patient 01-011 (0.742), Patient 21-003 (0.911), Patient 21-008 (0.647), and Patient 21-010 (0.423). These 4 patients suffered from nephropathic cystinosis and qualified for enrollment. The evidence is as follows: (1) Their WBC cystine levels varied higher than 1 nmol ½ cystine/mg protein, up to 1.618, 1.472, 1.381, and 4.954, respectively, during the study; and (2) They had documentations for the diagnosis of nephropathic cystinosis at baseline:

● Patient 01-011 (History of renal failure and anemia; ongoing cystinosis, abnormal renal function, decline in eGFR, persistent proteinuria, hypertension, hypothyroid, hypocalcemia, and hyperphosphatemia);
● Patient 21-003 (Microscopically diagnosed cystinosis with cystine crystals found in bone marrow aspiration, decline in eGFR, and abnormal renal function);
● Patient 21-008 (Genetically diagnosed cystinosis with multiple mutations in the CTNS gene, severe decline in eGFR to 26, persistent proteinuria, abnormal renal function, and anemia); and
● Patient 21-010 (Genetically diagnosed cystinosis with multiple mutations the CTNS gene, abnormal renal function, persistent proteinuria, mild decline in eGFR, and corneal cystine crystal cystine crystal deposition).

(2) Improvements of Growth Parameters

Growth data (standing height, weight, BMI, and BSA) were summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum); head circumference was not measured in this study. The observed value, change from baseline, and percentage change from baseline were included. The percentile and z-score (SD relative to a reference population for a subject's gender and age were also summarized; Tables 10 and 23). The percentile and z-score were calculated based on the Center for Disease Control and Prevention (CDC) growth data for the general population. Height (adjusted for each subject's gender and age) was obtained by following the 6 steps at the CDC website: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm.

Table 10: Summary of Percentile and Z-Score for Weight and Adjusted Standing Height in Subjects Less Than 6 Years of Age (Study RP103-08)

Visit	Weight Percentile Mean (SD)	Weight Z-score Mean (SD)	Height Percentile Mean (SD)	Height Z-score Mean (SD)
Day 1 (n=14)	3.46 (11.13)	-3.98 (2.07)	2.59 (4.00)	-3.16 (1.55)
Month 6 (n=14)	10.12 (18.31)	-2.83 (2.25)	14.69 (20.51)	-2.05 (1.68)
Month 9 (n=14)	12.37 (21.86)	-2.48 (2.14)	25.84 (29.09)	-1.40 (1.72)
Month 12 (n=13)	11.92 (18.30)	-2.22 (1.67)	32.66 (37.60)	-1.11 (1.88)
Month 18 (n=10)	30.05 (28.23)	-1.29 (1.95)	55.36 (43.88)	0.05 (2.07)

Source: Study RP103-08 CSR Table 14.2.1.5.3 (Height) and Table 14.2.1.7.3 (Weight).
SD=standard deviation
From Section 1.11.3 Clinical Information Amendment on November 2, 2017.

Standing Height

Because of the small size of trial and the large variations of data collection, these data are not appropriate for the label. These data only show the trends of clinical stabilization and improvement.

The mean z-scores, based on CDC growth charts as a reference population, were negative values from Day 1 through Month 15, then positive values thereafter (Table 11). The mean (± SD) z-scores were -3.16 ±1.55 at Day 1, -2.94 ±1.49 at the first on-treatment assessment (Week 2), -2.52 ±1.53 at the last Bi-Monthly Visit (Week 12), 0.05 ±2.07 at the last Quarterly Visit (Month 18), and 0.11 ±1.96 at Study Exit.

On Day 1, standing height (mean ± SD) was in the 2.59 ±4.00 percentile of the reference population (Table 11). The mean percentile was 3.27 ±5.69 at the first on-treatment assessment (Week 2), 6.95 ±10.88 at the last Bi-Monthly Visit (Week 12), and 55.36 ±43.88 at the last Quarterly Visit (Month 18). At Study Exit, the mean percentile was 50.52 ±40.46.

Table 11: Summary of Percentile and Z-score for Adjusted Standing Height (Subjects Age <6 Years)

Visit		Subjects Age <6 Years (N=15)	
		Percentile	Z-score
Day 1	N	14	14
	Mean (SD)	2.59 (4.00)	-3.16 (1.55)
	Median	0.08	-3.18
	Min, Max	0.00, 10.70	-5.82, -1.24
Week 2	N	15	15
	Mean (SD)	3.27 (5.69)	-2.94 (1.49)
	Median	0.18	-2.91
	Min, Max	0.00, 18.41	-6.07, -0.90
Week 4	N	13	13
	Mean (SD)	2.23 (3.49)	-3.02 (1.43)
	Median	0.18	-2.91
	Min, Max	0.00, 9.55	-5.93, -1.31
Week 6	N	14	14
	Mean (SD)	3.06 (4.65)	-2.83 (1.41)
	Median	0.27	-2.79
	Min, Max	0.00, 13.98	-5.74, -1.08
Week 8	N	14	14
	Mean (SD)	4.73 (7.21)	-2.69 (1.52)
	Median	1.07	-2.31
	Min, Max	0.00, 22.33	-5.69, -0.76
Week 10	N	13	13
	Mean (SD)	4.56 (6.68)	-2.76 (1.58)
	Median	0.82	-2.40
	Min, Max	0.00, 21.39	-5.55, -0.79
Week 12	N	14	14
	Mean (SD)	6.95 (10.88)	-2.52 (1.53)
	Median	1.03	-2.33
	Min, Max	0.00, 32.83	-5.33, -0.44

(Continued)

Visit		Subjects Age <6 Years (N=15)	
Month 6	N	14	14
	Mean (SD)	14.69 (20.51)	-2.05 (1.68)
	Median	2.13	-2.05
	Min, Max	0.00, 57.05	-5.22, 0.18
Month 9	N	14	14
	Mean (SD)	25.84 (29.09)	-1.40 (1.72)
	Median	9.65	-1.30
	Min, Max	0.00, 80.96	-4.69, 0.88
Month 12	N	13	13
	Mean (SD)	32.66 (37.60)	-1.11 (1.88)
	Median	8.60	-1.37
	Min, Max	0.00, 95.58	-4.34, 1.70
Month 15	N	11	11
	Mean (SD)	39.79 (40.64)	-0.71 (1.90)
	Median	19.63	-0.85
	Min, Max	0.00, 97.53	-3.95, 1.97
Month 18	N	10	10
	Mean (SD)	55.36 (43.88)	0.05 (2.07)
	Median	67.31	0.57
	Min, Max	0.01, 98.79	-3.75, 2.25
Study Exit	N	14	14
	Mean (SD)	50.52 (40.46)	0.11 (1.96)
	Median	38.94	-0.28
	Min, Max	0.01, 99.90	-3.83, 3.08

Source: Table 14.2.1.5.3.
Max = maximum; Min = minimum; SD = standard deviation.
Note: Subjects more than 20 years old were excluded from this analysis.

From Study Report RP103-08 Pages 81-82; Individual height and weight Z-scores are at Table 23.

Weight

Because of the small size of trial and the large variations of data collection, these data are not appropriate for the label. These data only show the trends of clinical stabilization and improvement.

The mean z-scores, according to CDC growth charts as a reference population, were decreasing negative values over the course of the study. The mean (± SD) z-scores were -3.98 ±2.07 at Day 1, -3.92 ±2.10 at the first on-treatment assessment (Week 2), -3.31 ±2.06 at the last Bi-Monthly Visit (Week 12), -1.29 ±1.95 at the last Quarterly Visit (Month 18), and -1.10 ±1.78 at Study Exit.

On Day 1, weight (mean ± SD) was in the 3.46 ±11.13 percentile of the reference population. The mean percentile was 3.41 ±10.78 at the first on-treatment assessment (Week 2), 5.38 ±13.89 at the last Bi-Monthly Visit (Week 12), and 30.05 ±28.23 at the last Quarterly Visit (Month 18). At Study Exit, the mean percentile for standing weight was 32.85 ±35.58.

Table 12: Summary of Percentile and Z-score for Weight (Age <6 Years), Mean (SD)

Visit	Number of Patients	Percentile	Z-score
Day 1	14	3.46 (11.13)	-3.98 (2.07)
Week 2	15	3.41 (10.78)	-3.92 (2.10)
Week 12	14	5.38 (13.89)	-3.31 (2.06)

Month 18	10	30.05 (28.23)	-1.29 (1.95)
Study Exit	14	32.85 (35.58)	-1.10 (1.78)

Note: Study Exit had 10 subjects who completed 18 months' treatment, and 4 subjects who completed 12 months' treatment. From Study Report of RP103-08, Pages 85 to 87; Individual height and weight Z-scores are at Table 23.

Body Mass Index

The mean z-scores for BMI, based on CDC growth charts as a reference population, were small negative values at each visit (Table 13). At Day 1, the mean (± SD) z-score was -1.03 ±1.14. The mean z-scores were -1.19 ±1.27 at the first on-treatment assessment (Week 2), -0.85 ±1.20 at the last Bi-Monthly Visit (Week 12), -1.78 ±1.13 at the last Quarterly Visit (Month 18), and -1.23 ±1.30 at Study Exit.

Mean percentile based on the reference population remained stable over the course of the study (Table 13). On Day 1, BMI (mean ± SD) was in the 22.44 ±27.83 percentile of the reference population. The mean percentile was 19.77 ±31.08 at the first on-treatment assessment (Week 2), 27.55 ±31.27 at the last Bi-Monthly Visit (Week 12), and 10.55 ±11.78 at the last Quarterly Visit (Month 18). At Study Exit, the mean percentile was 21.57 ±28.19, which was similar to that on Day 1.

Table 13: Summary of Percentile and Z-score for Adjusted Body Mass Index (Subjects Age <6 Years)

Visit		Subjects Age <6 Years (N=15)	
		Percentile	Z-score
Day 1	N	8	8
	Mean (SD)	22.44 (27.83)	-1.03 (1.14)
	Median	15.28	-1.03
	Min, Max	0.21, 88.12	-2.86, 1.18
Week 2	N	8	8
	Mean (SD)	19.77 (31.08)	-1.19 (1.27)
	Median	7.36	-1.48
	Min, Max	0.48, 93.54	-2.59, 1.52
Week 4	N	6	6
	Mean (SD)	8.09 (8.49)	-1.75 (0.89)
	Median	5.72	-1.60
	Min, Max	0.05, 22.74	-3.27, -0.75
Week 6	N	7	7
	Mean (SD)	20.70 (31.61)	-1.18 (1.26)
	Median	7.75	-1.42
	Min, Max	0.62, 89.53	-2.50, 1.26
Week 8	N	7	7
	Mean (SD)	23.49 (30.84)	-0.97 (1.15)
	Median	11.93	-1.18
	Min, Max	0.90, 89.64	-2.37, 1.26
Week 10	N	6	6
	Mean (SD)	22.92 (33.36)	-1.05 (1.26)
	Median	12.82	-1.19
	Min, Max	0.99, 89.08	-2.33, 1.23
Week 12	N	7	7
	Mean (SD)	27.55 (31.27)	-0.85 (1.20)
	Median	25.19	-0.67
	Min, Max	1.83, 90.39	-2.09, 1.30

(Continued)

Visit		Subjects Age <6 Years (N=15)	
Month 6	N	7	7
	Mean (SD)	36.13 (32.06)	-0.61 (1.30)
	Median	28.81	-0.56
	Min, Max	0.19, 87.09	-2.89, 1.13
Month 9	N	7	7
	Mean (SD)	24.65 (28.65)	-1.05 (1.37)
	Median	14.90	-1.04
	Min, Max	0.02, 86.27	-3.55, 1.09
Month 12	N	6	6
	Mean (SD)	15.46 (16.29)	-1.62 (1.51)
	Median	11.81	-1.21
	Min, Max	0.00, 43.95	-4.44, -0.15
Month 15	N	6	6
	Mean (SD)	18.21 (18.36)	-1.27 (1.04)
	Median	15.51	-1.10
	Min, Max	0.15, 48.61	-2.97, -0.03
Month 18	N	6	6
	Mean (SD)	10.55 (11.78)	-1.78 (1.13)
	Median	7.23	-1.47
	Min, Max	0.06, 30.10	-3.26, -0.52
Study Exit	N	7	7
	Mean (SD)	21.57 (28.19)	-1.23 (1.30)
	Median	9.62	-1.30
	Min, Max	0.04, 78.06	-3.37, 0.77

Source: Table 14.2.1.9.2.
Max = maximum; Min = minimum; SD = standard deviation.
Note: Subjects more than 20 years old and less than 2 years old were excluded from this analysis.

From Study Report RP103-08, Pages 90-91.

Body Surface Area

The mean z-scores (weight-for-height) based on CDC growth charts as a reference population, were negative values at each visit (Table 14). At Day 1, the mean (± SD) z-score was -1.79 ±1.13. The mean z-scores were -1.95 ±1.19 at the first on-treatment assessment (Week 2), -1.59 ±1.16 at the last Bi-Monthly Visit (Week 12), and -1.51 ±1.12 at the last Quarterly Visit (Month 18). At Study Exit, the mean z-score was -1.26 ±1.11.

The mean percentile of adjusted weight-for-height based on the reference population is also presented in (Table 14). On Day 1, BSA (mean ± SD) was in the 10.87 ±21.26 percentile of the reference population. The mean percentile was 9.97 ±22.53 at the first on-treatment assessment (Week 2), 14.29 ±23.16 at the last Bi-Monthly Visit (Week 12), and 14.17 ±12.96 at the last Quarterly Visit (Month 18). At Study Exit, the mean percentile of weight-for-height was 19.41 ±23.96.

Table 14: Summary of Percentile and Z-score for Adjusted Weight-for-Height (Subjects Age <6 Years)

Visit		Subjects Age <6 Years (N=15)	
		Percentile	Z-score
Day 1	N	14	14
	Mean (SD)	10.87 (21.26)	-1.79 (1.13)
	Median	5.18	-1.63
	Min, Max	0.02, 82.67	-3.49, 0.94
Week 2	N	15	15
	Mean (SD)	9.97 (22.53)	-1.95 (1.19)
	Median	1.70	-2.12
	Min, Max	0.02, 89.21	-3.57, 1.24
Week 4	N	13	13
	Mean (SD)	6.98 (9.27)	-2.03 (1.03)
	Median	3.32	-1.84
	Min, Max	0.01, 32.28	-3.82, -0.46
Week 6	N	14	14
	Mean (SD)	11.98 (21.71)	-1.85 (1.25)
	Median	2.66	-1.95
	Min, Max	0.00, 82.35	-3.96, 0.93

(Continued)

Visit		Subjects Age <6 Years (N=15)	
Week 8	N	14	14
	Mean (SD)	13.12 (21.98)	-1.64 (1.11)
	Median	4.49	-1.71
	Min, Max	0.14, 84.38	-2.99, 1.01
Week 10	N	13	13
	Mean (SD)	17.03 (25.55)	-1.49 (1.21)
	Median	8.11	-1.40
	Min, Max	0.12, 83.82	-3.04, 0.99
Week 12	N	14	14
	Mean (SD)	14.29 (23.16)	-1.59 (1.16)
	Median	7.15	-1.47
	Min, Max	0.09, 87.06	-3.12, 1.13
Month 6	N	14	14
	Mean (SD)	18.29 (25.93)	-1.42 (1.25)
	Median	6.66	-1.51
	Min, Max	0.04, 86.08	-3.37, 1.08
Month 9	N	14	14
	Mean (SD)	13.46 (22.88)	-1.62 (1.19)
	Median	5.87	-1.57
	Min, Max	0.01, 87.60	-3.79, 1.15
Month 12	N	13	13
	Mean (SD)	14.63 (20.67)	-1.64 (1.27)
	Median	5.37	-1.61
	Min, Max	0.00, 68.30	-4.42, 0.48
Month 15	N	11	11
	Mean (SD)	14.69 (15.92)	-1.39 (0.91)
	Median	5.75	-1.58
	Min, Max	0.07, 51.59	-3.19, 0.04
Month 18	N	10	10
	Mean (SD)	14.17 (12.96)	-1.51 (1.12)
	Median	14.56	-1.06
	Min, Max	0.01, 39.81	-3.70, -0.26

(Continued)

Visit		Subjects Age <6 Years (N=15)	
Study Exit	N	14	14
	Mean (SD)	19.41 (23.96)	-1.26 (1.11)
	Median	10.54	-1.26
	Min, Max	0.04, 82.76	-3.33, 0.94

Source: Table 14.2.1.11.2.
Max = maximum; Min = minimum; SD = standard deviation.
Note: Subjects with height <45 cm or >121 cm were excluded from this analysis.
From Study Report RP103-08, Pages 94-96.

Handling of Dropouts or Missing Data

All data recorded on the CRF were included. There were no substitutions made to accommodate missing data points.

Data Sets Analyzed

Safety Population: All subjects who received at least 1 dose of Procysbi. The Safety Population was used for the analysis of demographic/baseline characteristics, medical history, study drug exposure, and safety endpoints. The numbers of the 17 subjects included in each age subgroup were as follows:

- 1.04 years to 1.89 years: 7 subjects;
- 2.28 years to 4.53 years: 8 subjects;
- >6 years: one subject 9.03 years; one subject 22.26 years.

PD Population: All subjects who received at least 1 dose of Procysbi and who had at least 1 WBC cystine level recorded. The PD Population was used for analysis of demographic/baseline characteristics, WBC cystine level data, and growth parameters. The numbers of the 17 subjects included in each age subgroup were the same as the Safety Population.

PK Population: All subjects who received at least 1 dose of Procysbi and who had available PK data. The PK Population was used for the analysis of demographic/baseline characteristics and PK parameters. The numbers of the 17 subjects included in each age subgroup were the same as the Safety Population.

Protocol Amendments

There were 2 amendments. The Applicant provided the rationale for amendment. All the changes were reviewed. These modifications did not change the integrity of the trial or reviewer's interpretation of the results.

Data Quality Assurance

The Applicant assured the data quality and integrity of Study RP103-08. The study was conducted in accordance with Good Clinical Practice (GCP) as required by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

All study protocol amendments, written study patient information, informed consent form (ICF), and any other appropriate study-related information were reviewed and received approval of ethics committee (i.e., Institutional Review Board [IRB], and Independent Ethics Committee [IEC]) before the study began. Institutional Review Board/IEC information for all study sites is submitted.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable to this review, because there was only one trial submitted (Study RP103-08); see Section 6.1 of this Review.

7.1.1. Study Endpoints

This section is not applicable to this review, because there was only one trial submitted (Study RP103-08); see Section 6.1.1 of this Review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Potential differences in efficacy in different populations were not studied.

7.2.2. Other Relevant Benefits

More convenient dosing schedule or route of administration were not evaluated.

7.3. Integrated Assessment of Effectiveness

Nephropathic cystinosis is a life-threatening rare disease. In a retrospective study of 205 untreated patients, the median survival time was 8.5 years. The median time for "renal death" (defined as uremia requires renal replacement therapy) was 9.2 years. The youngest patient dying of renal death was 5.2 years (Gretz, 1982). The primary pathology is known as the accumulation of free cystine in lysosomes, eventually leading to intracellular crystal formation that disturbs cellular oxidative metabolism, glutathione status, and mitochondrial energy production.

Study RP103-08 shows that Procysbi decreased the mean cystine concentration of white blood cell from 3.1 (Day 1) to 0.8 nmol ½ cystine/mg protein (Month 12). The proportion of patients who had low WBC cystine (< 1.0 nmol ½ cystine/mg protein) was increased from 20% (Day 1) to 61% (Month 12). The renal function was stabilized as measured by eGFR, a 14% increase from baseline. The mean height of patients increased from 2.5 percentile (Day 1) to 50.5 percentile at Study Exit (10 patients completed 18-month treatment and 3 patients completed 12-month treatment). This increase correlates with Z-scores increase from -3.1 to 0.1 as determined by the CDC method adjusted for each subject's gender and age. The mean weight was increased from 3.4 percentile (Day 1) to 32.8 percentile (Study Exit), and Z-scores increased from -3.9 to -1.1.

These results are consistent with the previous submissions (Studies RP103-03 and RP103-04) supporting the effectiveness of Procysbi in treatment of the disease. From the clinical reviewer standpoint, the Written Request issued on August 19, 2013 is fulfilled.

8. Review of Safety

8.1. Safety Review Approach

The safety review is based on Study RP103-08. It focuses on the 15 subjects age <6 years. The safety review includes treatment-emergent SAEs, the most common AEs, clinical laboratory test (hematology, chemistry, and urinalysis), physical examinations, vital signs, and 12-lead ECGs. These safety data were performed at the Screening, the 6 Bi-Monthly visits, the 3 Quarterly visits, and the Study Exit.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Starting dose and maintenance dose

The overall cysteamine exposure was lower in subjects <6 years (Study RP103-08) as compared to the older children (>6 years) and adults (Study RP103-03). Procysbi dose was individually titrated based on tolerability and response.

According to the Procysbi label, the initial dosage in Cysteamine-naïve patients was 1/6 to 1/4 of the maintenance dose and was adjusted based on the subject's age, weight, and body surface area (BSA). The maintenance dose was 1 gram/m^2/day, in 2 divided doses given every 12 hours. The dose was gradually escalated (10% steps, every 2 weeks) until the subject's WBC cystine level was <1 nmol ½ cystine/mg protein.

Table 15: Weight-adjusted maintenance dose of Procysbi in Children Age <6 years

Weight in Pounds	Weight in Kilograms	mg of Cysteamine Free Base* Every 12 Hours
0–10	0–5	200
11–20	5–10	300
21–30	11–15	400
31–40	16–20	500
41–50	21–25	600
51–70	26–30	700
71–90	31–40	800
91–110	41–50	900
>110	>50	1000

* The active ingredient in RP103 is cysteamine bitartrate; dosage is expressed as mg of cysteamine free base.

Extent of Exposure

For subjects age <6 years (N=15), the mean (± SD) number of days of study drug exposure was 511.7 ±158.1 (median 575.0 days; range 17-611 days). One subject completed 2 weeks of treatment, 4 subjects completed at least 12 months of treatment, and 10 subjects completed at least 18 months of treatment.

Table 16: Exposure to Study Drug (Safety Population and Subjects Age <6 Years)

Parameter	Subjects Age <6 Years (N=15)	All Subjects (N=17)
Duration of Study Drug Exposure (days)[1]		
N	15	17
Mean (SD)	511.7 (158.11)	493.5 (156.63)
Median	575.0	575.0
Min, Max	17, 611	17, 611
Days with a missed dose		
N	15	17
Mean (SD)	3.9 (7.52)	3.5 (7.12)
Median	1.0	1.0
Min, Max	0, 29	0, 29
Subjects completing dosing, n (%)		
Day 1	15 (100.0)	17 (100.0)
Week 2	15 (100.0)	17 (100.0)
Week 4	14 (93.3)[2]	16 (94.1)[2]
Week 6	14 (93.3)	16 (94.1)
Week 8	14 (93.3)	16 (94.1)
Week 10	14 (93.3)	16 (94.1)
Week 12	14 (93.3)	16 (94.1)
Month 6	14 (93.3)	16 (94.1)
Month 9	14 (93.3)	16 (94.1)
Month 12	14 (93.3)	14 (82.4)[3,4]
Month 18	10 (66.7)	10 (58.8)

Source: Table 14.1.4, Table 14.1.4.3, Listing 16.2.1.1, and Listing 16.2.4.1.
From Study RP103-08 Report, Page 113.

8.2.2. **Relevant characteristics of the safety population:**

Demographics and baseline characteristics

Demographic and baseline characteristics are summarized in Table 5 (Section 6.1.2) for the age <6 years group. The mean (± SD) age was 2.2 ±0.9 years. Eight subjects (53.3%) were male. The majority were Hispanic or Latino (11 subjects, 73.3%). Mean weight was 9.0 ±2.0 kg, and mean height was 77.1 ±7.5 cm. Mean BMI was 14.9 ±1.2 kg/m^2, and mean BSA was 0.4 ±0.1 m^2. Using CDC growth charts as a reference population, mean z-scores were -3.9 ±2.0 for baseline weight, -3.1 ±1.5 for baseline height (based on an adjusted mean height of 77.5 ±7.1 cm, calculated per CDC methods), -1.0 ±1.1 for baseline BMI, and -1.7 ±1.1 for baseline BSA.

8.2.3. **Adequacy of the safety database:**

Nephropathic cystinosis is a rare disease. The estimated prevalence is 500 cases in the U.S. The size of the safety database is acceptable. The exposure to Procysbi, the duration of treatment, and the patient demographics are adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Important data quality issues that may influence the safety review were not found.

The safety review was based on Study RP103-08. The safety database was collected from the 6 Bi-Monthly visits, the 3 Quarterly visit, and the Study Exit visit. Adverse events were collected at the weekly and/or monthly clinical visits. The data integrity and submission quality are acceptable. Assessment of the consistency of data did not identify safety issues.

OSI (Office of Scientific Investigations) did not audit this submission. OCS (Office of Computational Science) did not conduct data fitness assessment.

8.3.2. Categorization of Adverse Events

The Applicant's approach to categorization of adverse events is reasonable.

- The Applicant provided adequate definition of AEs and serious adverse events in the protocols.
- The definition of TEAE (treatment emergent adverse events) was appropriate.
- MedDRA (Versions 16.1) was used to code AEs.
- AEs were collected at the clinical visits.
- AEs and SAEs were followed up until events returned to baseline.
- The AE assessment methods were appropriate.

8.3.3. Routine Clinical Tests

The routine clinical tests included hematology, chemistry and urinalysis. The safety database was collected from the 6 Bi-Monthly visits, the 3 Quarterly visits, and the Study Exit visit. Adverse events were collected at the weekly and/or monthly clinical visits. Clinically significant laboratory values, as well as clinically significant shifts in laboratory values, were required to be reported as TEAEs per study protocols. The assessment methods and time points of routine laboratory evaluations were reasonable.

8.4. Safety Results

8.4.1. Deaths

There was one patient who died during Study RP103-08. The cause of death was

gastroenteritis, vomiting, and diarrhea. The investigator stated that the death was not related to Procysbi treatment.

> Patient 21-007 was a 3-year old Black male with nephropathic cystinosis and Fanconi syndrome. He received 50 mg of Procysbi, P.O. bid on Day 1, and took concomitant medications: calcitriol, calcium carbonate, ergocalciferol, magnesium sulfate, phosphorus, potassium chloride, ranitidine, sodium bicarbonate, and sodium chloride. On Day 16, he experienced gastroenteritis, vomiting, and diarrhea, and developed hypovolemic shock, and cardiopulmonary failure. The patient died in the hospital on Day 17. The investigator stated the death was not related to Procysbi treatment, but likely related to the underlying condition.

Medical Officer Comments:
I agree with the investigator that direct evidence of a causative relationship of Procysbi treatment and the death is not found. There was no evidence of vomiting when Procysbi was started.

8.4.2. **Serious Adverse Events**

The most frequently reported SAEs (by SOC) were Infections and Infestations (8/17 subjects, 47.1%), Metabolism and Nutrition Disorders (7/17 subjects, 41.2%), and Gastrointestinal Disorders (5/17 subjects, 29.4%). The most frequently reported individual SAEs (≥10% of subjects; by PT) were gastroenteritis (5/17 subjects, 29.4%), dehydration and vomiting (4/17 subjects, 23.5% each). All the vomiting SAEs occurred in subjects age <6 years (4/15 subjects, 26.6 %).

Table 17: Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term[1]	Titration[2] (N=17) n (%)	Maintenance[2] (N=15) n (%)	Overall (N=17) n (%)
Subjects with Any SAE	**6 (35.3)**	**8 (53.3)**	**12 (70.6)**
Infections and Infestations	**3 (17.6)**	**5 (33.3)**	**8 (47.1)**
Gastroenteritis	2 (11.8)	3 (20.0)	5 (29.4)
Catheter Site Infection	0	1 (6.7)	1 (5.9)
Clostridium difficile Colitis	0	1 (6.7)	1 (5.9)
Gastroenteritis Viral	1 (5.9)	0	1 (5.9)
Metabolism and Nutrition Disorders	**2 (11.8)**	**5 (33.3)**	**7 (41.2)**
Dehydration	1 (5.9)	3 (20.0)	4 (23.5)
Electrolyte Imbalance	0	2 (13.3)	2 (11.8)
Failure to Thrive	1 (5.9)	0	1 (5.9)
Hypernatraemia	0	1 (6.7)	1 (5.9)
Hypocalcaemia	0	1 (6.7)	1 (5.9)
Malnutrition	0	1 (6.7)	1 (5.9)
Metabolic Acidosis	0	1 (6.7)	1 (5.9)
Gastrointestinal Disorders	**1 (5.9)**	**4 (26.7)**	**5 (29.4)**
Vomiting	1 (5.9)	3 (20.0)	4 (23.5)
Abdominal Distension	0	1 (6.7)	1 (5.9)
Surgical and Medical Procedure	**0**	**2 (13.3)**	**2 (11.8)**
Gastrostomy	0	2 (13.3)	2 (11.8)
Blood and Lymphatic System Disorders	**1 (5.9)**	**0**	**1 (5.9)**
Anaemia	1 (5.9)	0	1 (5.9)
Cardiac Disorders	**1 (5.9)**	**0**	**1 (5.9)**
Cardiopulmonary Failure	1 (5.9)	0	1 (5.9)
Congenital, Familial and Genetic Disorders	**1 (5.9)**	**0**	**1 (5.9)**
Fanconi Syndrome	1 (5.9)	0	1 (5.9)
Vascular Disorders	**1 (5.9)**	**0**	**1 (5.9)**
Hypovolaemic Shock	1 (5.9)	0	1 (5.9)

Source: Table 14.3.2.2.1, Table 14.3.2.2.2, and Listing 16.2.4.1.
MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
Note: If a subject experienced more than 1 event in a given SOC, that subject was counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject was counted only once for that PT.
Note: All subjects with SAEs were age <6 years.
[1] Coded using MedDRA version 16.1.
[2] A subject entered the Maintenance period when dose adjustments ceased.

From Study RP103-08 Report, Page 130.

8.4.3. **Dropouts and/or Discontinuations Due to Adverse Effects**

There was one patient discontinued from the study due to death (see Section 8.4.1). There was

no non-fatal treatment discontinuation.

8.4.4. Significant Adverse Events

There were 5 (5/15) subjects who had Grade ≥3 treatment-emergent adverse events.

Table 18: Treatment-Emergent Adverse Events Grade ≥3, by MedDRA System Organ Class and Preferred Term (Subjects Age <6 Years)

System Organ Class Preferred Term[1]	Subjects Age <6 Years (N=15)		
	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Subjects with Any TEAE Grade ≥3	**4 (26.7)**	**0**	**1 (6.7)**
Infections and Infestations	**1 (6.7)**	**0**	**1 (6.7)**
Gastroenteritis	0	0	1 (6.7)
Gastroenteritis Viral	1 (6.7)	0	0
Metabolism and Nutrition Disorders	**2 (13.3)**	**0**	**0**
Failure to Thrive	1 (6.7)	0	0
Hypernatraemia	1 (6.7)	0	0
Blood and Lymphatic System Disorders	**1 (6.7)**	**0**	**0**
Anaemia	1 (6.7)	0	0
Cardiac Disorders	**0**	**0**	**1 (6.7)**
Cardiopulmonary Failure	0	0	1 (6.7)
Congenital, Familial and Genetic Disorders	**0**	**0**	**1 (6.7)**
Fanconi Syndrome	0	0	1 (6.7)
Vascular Disorders	**0**	**0**	**1 (6.7)**
Hypovolaemic Shock	0	0	1 (6.7)

Source: Table 14.3.1.4.3.
MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: If a subject experienced more than 1 event in a given SOC, that subject was counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject was counted only once for that PT.
Note: None of the TEAEs Grade ≥3 was considered related to the study drug (Table 12-8).
[1] Coded using MedDRA version 16.1.

From Study RP103-08 Report, Page124.

Study RP103-08 shows 13/15 (86.6%) patients have vomiting during the study. SAE vomiting patients were 5/15 (33.3%) and non-SAE vomiting patients were 8/15 (53.3%).

Table 19: Vomiting Severity in Patients <6 years

Patient ID	Age (Year)	Concomitant PPI	Vomiting Status
01-009	1.6	None	Vomiting (non-SAE)
01-010	1.2	None	No vomiting

01-012	2.4	None	SAE vomiting
01-013	1.1	None	SAE vomiting
21-001	4.5	Omeprazole	Vomiting (non-SAE)
21-002	1.8	Omeprazole	No vomiting
21-003	1.9	None	Vomiting (non-SAE)
21-004	2.6	Omeprazole	Vomiting (non-SAE)
21-005	2.3	Omeprazole	Vomiting (non-SAE)
21-006	2.3	None	SAE vomiting
21-007	3.7	None	SAE vomiting and death
21-008	2.4	Omeprazole	Vomiting (non-SAE)
21-009	3.1	Omeprazole	Vomiting (non-SAE)
21-010	1.0	Omeprazole	Vomiting (non-SAE)
21-011	1.4	Omeprazole	SAE vomiting

Note: From the clinical reviewer notes based on Study RP103-08 Report.

Medical Officer Comments:
Cysteamine is a mercaptoethylamine compound that is endogenously derived from the coenzyme A degradative pathway. As a metabolic degradative product (aminothiol), cysteamine can stimulate gastric and other viscera vagal afferent nerves as well as sympathetic afferent nerves. Also, it can stimulate the chemoreceptor trigger zone located at area postrema (the floor of the fourth ventricle). These effects activate the CNS functional vomiting center at the medulla, and trigger nausea and vomiting. It appears that treatment naïve patients age <6 years (Study RP103-08) were more susceptible to cysteamine-induced vomiting (13/15, 86%) than the patients previously treated with cysteamine in Study RP103-03 (age >6 years: 26/40, 65%; and age ≤6 years: 8/13, 62%). Cysteamine-induced nausea and vomiting can be clinically managed. The benefit/risk ratio of Procysbi treatment is not changed for treatment naïve patients age <6 years. There were 8 patients who had concomitant usage of omeprazole (Table 19). One patient (ID 21-002) who used omeprazole along with Procysbi did not have vomiting; Four patients (IDs 01-012, 01-013, 21-006 and 21-007) who did not use PPI, but Procysbi, had SAE vomiting. These results do not appear to support that PPI plays a role in Procysbi-induced vomiting.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

All the treatment-emergent AEs are listed in Table 20 below.

Table 20: Treatment-Emergent Adverse Events by Study Period, by MedDRA System Organ Class and Preferred Term (Subjects Age <6 Years)

System Organ Class Preferred Term[1]	Titration[2] (N=15) n (%)	Maintenance[2] (N=14) n (%)	Overall (N=15) n (%)
Subjects with Any TEAE	**15 (100)**	**14 (100)**	**15 (100)**
Infections and Infestations	**9 (60.0)**	**12 (85.7)**	**15 (100)**
Upper Respiratory Tract Infection	2 (13.3)	7 (50.0)	8 (53.3)
Gastroenteritis	2 (13.3)	5 (35.7)	7 (46.7)
Rhinitis	3 (20.0)	0	3 (20.0)
Catheter Site Infection	0	1 (7.1)	1 (6.7)
Clostridium difficile Colitis	0	1 (7.1)	1 (6.7)
Gastroenteritis Viral	1 (6.7)	0	1 (6.7)
Otitis Media	1 (6.7)	1 (7.1)	1 (6.7)
Pharyngitis	0	1 (7.1)	1 (6.7)
Sinusitis	0	1 (7.1)	1 (6.7)
Varicella	0	1 (7.1)	1 (6.7)
Gastrointestinal Disorders	**12 (80.0)**	**9 (64.3)**	**13 (86.7)**
Vomiting	8 (53.3)	7 (50.0)	12 (80.0)
Diarrhoea	4 (26.7)	3 (21.4)	5 (33.3)
Breath Odour	3 (20.0)	0	3 (20.0)
Nausea	2 (13.3)	1 (7.1)	3 (20.0)
Abdominal Distension	0	1 (7.1)	1 (6.7)
Abdominal Pain	0	1 (7.1)	1 (6.7)
Metabolism and Nutrition Disorders	**3 (20.0)**	**5 (35.7)**	**7 (46.7)**
Dehydration	1 (6.7)	3 (21.4)	4 (26.7)
Electrolyte Imbalance	0	2 (14.3)	2 (13.3)
Failure to Thrive	1 (6.7)	0	1 (6.7)
Hypernatraemia	1 (6.7)	1 (7.1)	1 (6.7)
Hypocalcaemia	0	1 (7.1)	1 (6.7)
Hypokalaemia	1 (6.7)	0	1 (6.7)
Malnutrition	0	1 (7.1)	1 (6.7)
Metabolic Acidosis	0	1 (7.1)	1 (6.7)

(Continued)

System Organ Class Preferred Term[1]	Titration[2] (N=15) n (%)	Maintenance[2] (N=14) n (%)	Overall (N=15) n (%)
General Disorders and Administration Site Conditions	**1 (6.7)**	**4 (28.6)**	**5 (33.3)**
Pyrexia	1 (6.7)	3 (21.4)	4 (26.7)
Granuloma	0	1 (7.1)	1 (6.7)
Medical Device Site Reaction	1 (6.7)	0	1 (6.7)
Respiratory, Thoracic and Mediastinal Disorders	**5 (33.3)**	**0**	**5 (33.3)**
Cough	4 (26.7)	0	4 (26.7)
Rhinorrhoea	2 (13.3)	0	2 (13.3)
Epistaxis	1 (6.7)	0	1 (6.7)
Surgical and Medical Procedures	**1 (6.7)**	**2 (14.3)**	**3 (20.0)**
Gastrostomy	0	2 (14.3)	2 (13.3)
Gastrostomy Closure	0	1 (7.1)	1 (6.7)
Gastrostomy Tube Removal	1 (6.7)	0	1 (6.7)
Eye Disorders	**0**	**2 (14.3)**	**2 (13.3)**
Conjunctivitis	0	1 (7.1)	1 (6.7)
Strabismus	0	1 (7.1)	1 (6.7)
Nervous System Disorders	**0**	**2 (14.3)**	**2 (13.3)**
Headache	0	2 (14.3)	2 (13.3)
Skin and Subcutaneous Tissue Disorders	**0**	**2 (14.3)**	**2 (13.3)**
Dermatitis Diaper	0	2 (14.3)	2 (13.3)
Blood and Lymphatic System Disorders	**1 (6.7)**	**0**	**1 (6.7)**
Anaemia	1 (6.7)	0	1 (6.7)
Cardiac Disorders	**1 (6.7)**	**0**	**1 (6.7)**
Cardiopulmonary Failure	1 (6.7)	0	1 (6.7)
Congenital, Familial and Genetic Disorders	**1 (6.7)**	**0**	**1 (6.7)**
Fanconi Syndrome	1 (6.7)	0	1 (6.7)
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (7.1)**	**1 (6.7)**
Foot Deformity	0	1 (7.1)	1 (6.7)

(Continued)

System Organ Class Preferred Term[1]	Titration[2] (N=15) n (%)	Maintenance[2] (N=14) n (%)	Overall (N=15) n (%)
Reproductive System and Breast Disorders	**0**	**1 (7.1)**	**1 (6.7)**
Perineal Erythema	0	1 (7.1)	1 (6.7)
Vascular Disorders	**1 (6.7)**	**0**	**1 (6.7)**
Hypovolaemic Shock	1 (6.7)	0	1 (6.7)

Source: Table 14.3.1.2.3.
MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: If a subject experienced more than 1 event in a given SOC, that subject was counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject was counted only once for that PT.
[1] Coded using MedDRA version 16.1.
[2] A subject entered the Maintenance period when dose adjustments ceased.

From Study RP103-08 Report, Pages 121-123.

8.4.6. **Laboratory Findings**

Laboratory evaluations included hematology, chemistry and urinalysis that were performed at screening, every Bi-Monthly Visit, each Quarterly Visit, and the Study Exit Visit. In general, for subjects age <6 years, the median changes from baseline were small, and no clinically significant trends were observed. The estimated GFR was a pertinent laboratory test. It is summarized as follows:

Estimated Glomerular Filtration Rate

Among the 15 subjects who were <6 years of age, the mean (± SD) eGFR was 55.93 ±22.43 mL/min/1.73 m^2 at baseline. The mean change from baseline was -0.15 ±13.30 mL/min/1.73 m^2 at the first on-treatment laboratory assessment (Week 2), 3.67 ±5.57 mL/min/1.73 m^2 at the last Bi-Monthly laboratory assessment (Week 10), and 11.20 ±17.25 mL/min/1.73 m^2 at the last Quarterly laboratory assessment (Month 18). At Study Exit, the mean eGFR was 63.79 ±21.44 mL/min/1.73 m^2, with a mean change from baseline of 8.14 ±15.48 mL/min/1.73 m^2.

Table 21: Summary of Estimated Glomerular Filtration Rate and Change from Baseline (Subjects Age <6 Years and Safety Population)

Visit		Subjects Age <6 Years (N=15)		Safety Population (N=17)	
		Observed (mL/min/1.73 m^2)	Change from Baseline (mL/min/1.73 m^2)	Observed (mL/min/1.73 m^2)	Change from Baseline (mL/min/1.73 m^2)
Baseline	N	15		17	
	Mean (SD)	55.93 (22.43)		56.24 (21.00)	
	Median	60.00		60.00	
	Min, Max	26.00, 112.00		26.00, 112.00	
Week 2	N	13	13	15	15
	Mean (SD)	57.62 (19.35)	-0.15 (13.30)	58.07 (17.97)	0.20 (12.35)
	Median	68.00	0.00	63.00	2.00
	Min, Max	25.00, 75.00	-37.00, 15.00	25.00, 75.00	-37.00, 15.00
Week 6	N	14	14	16	16
	Mean (SD)	55.43 (17.41)	-0.21 (11.62)	56.00 (16.32)	0.00 (10.84)
	Median	57.00	2.00	60.00	2.00
	Min, Max	28.00, 75.00	-37.00, 12.00	28.00, 75.00	-37.00, 12.00
Week 10	N	12	12	14	14
	Mean (SD)	53.83 (17.72)	3.67 (5.57)	54.57 (16.42)	3.21 (5.34)
	Median	53.50	2.00	56.00	1.50
	Min, Max	29.00, 75.00	-4.00, 12.00	29.00, 75.00	-4.00, 12.00
Month 6	N	11	11	13	13
	Mean (SD)	61.27 (15.47)	2.27 (16.70)	59.77 (14.62)	0.85 (15.72)
	Median	65.00	3.00	61.00	0.00
	Min, Max	27.00, 75.00	-37.00, 32.00	27.00, 75.00	-37.00, 32.00

(Continued)

Visit		Subjects Age <6 Years (N=15)		Safety Population (N=17)	
Month 9	N	14	14	16	16
	Mean (SD)	61.71 (23.43)	6.07 (12.33)	60.06 (22.40)	4.06 (13.05)
	Median	61.50	3.50	58.00	0.00
	Min, Max	27.00, 108.00	-10.00, 29.00	27.00, 108.00	-18.00, 29.00
Month 12	N	13	13	13	13
	Mean (SD)	60.92 (25.63)	6.77 (12.60)	60.92 (25.63)	6.77 (12.60)
	Median	56.00	6.00	56.00	6.00
	Min, Max	24.00, 115.00	-12.00, 25.00	24.00, 115.00	-12.00, 25.00
Month 15	N	11	11	11	11
	Mean (SD)	64.00 (27.98)	6.27 (16.47)	64.00 (27.98)	6.27 (16.47)
	Median	71.00	-3.00	71.00	-3.00
	Min, Max	26.00, 105.00	-11.00, 37.00	26.00, 105.00	-11.00, 37.00
Month 18	N	10	10	10	10
	Mean (SD)	67.20 (31.17)	11.20 (17.25)	67.20 (31.17)	11.20 (17.25)
	Median	77.00	6.50	77.00	6.50
	Min, Max	25.00, 107.00	-11.00, 37.00	25.00, 107.00	-11.00, 37.00
Study Exit	N	14	14	16	16
	Mean (SD)	63.79 (21.44)	8.14 (15.48)	61.50 (21.26)	5.50 (16.70)
	Median	68.50	6.50	68.00	3.00
	Min, Max	30.00, 93.00	-19.00, 33.00	30.00, 93.00	-25.00, 33.00

Source: Table 14.4.1.2 and Table 14.4.1.2.3.
Max = maximum; Min = minimum; SD = standard deviation.
Estimated glomerular filtration rate (mL/min/1.73 m^2) = 0.413*[Height (cm)/serum creatinine (mg/dL)].

From Study RP103-08 Report, Pages 132-133.

8.4.7. Vital Signs

Vital signs, height, and weight were recorded at each visit. In general, mean height, weight, and BSA increased over the study, as expected for this subject population, while mean BMI decreased slightly. For the other vital signs, mean changes from baseline were generally small, and there did not appear to be an adverse effect of the study drug over time.

Clinically significant changes in vital signs were to be recorded as TEAEs. Vital signs TEAEs were the following:

- Subject 01-008 (age 9 years) had a TEAE of hypertension. The onset of this TEAE occurred on Day 265 in the Maintenance period and was ongoing at the end of the study. The TEAE was nonserious, mild (Grade 1), and considered likely related to the cystinosis and not related to the study drug.

- Four subjects had TEAEs of pyrexia (01-010, 01-013, 21-005, and 21-009). One of these TEAEs was in the Titration period (age 1 year) and 3 were in the Maintenance period (ages 1 year, 2 years, and 3 years). The duration of pyrexia was 1-3 days for these TEAEs. All pyrexia cases were nonserious, mild (Grade 1), and considered unlikely related to cystinosis and not related to the study drug.

8.4.8. Electrocardiograms (ECGs)

Electrocardiograms were obtained at Screening and all Bi-Monthly Visits, all Quarterly Visits, and the Study Exit Visit.

Most ECGs were normal throughout the study. Three subjects had post-baseline abnormal not clinically significant ECGs: 2/16 subjects (12.5%) at Week 6 and 1/16 subjects (6.3%) at Week 10. No subject had an abnormal clinically significant ECG at any time during the study. There did not appear to be an adverse effect of study drug on ECGs, and there were no ECG-associated TEAEs reported.

8.4.9. QT

QT clinical trial was not conducted.

8.4.10. Immunogenicity

Immunogenicity study was not conducted.

8.5. Analysis of Submission-Specific Safety Issues

Clinical assessment of specific safety issue was not conducted.

8.6. Specific Safety Studies/Clinical Trials

Specific study to evaluate a specific safety concern was not conducted.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

There was no potential issue related to human carcinogenicity or tumor development identified.

8.7.2. Human Reproduction and Pregnancy

Human reproduction and pregnancy were not evaluated during the development program.

8.7.3. Pediatrics and Assessment of Effects on Growth

Written Request and Pediatric Exclusivity Determination
On August 19, 2013, FDA issued a Written Request of "A one-year open-label, PK/PD, Safety and Efficacy study in pediatric patients with nephropathic cystinosis aged birth to <6 years". The Written Request was amended on October 6, 2015.

Medical Officer Comments:
The Written Request and Study RP103-08 report were reviewed. Data on head circumference measurements for patients age <6 years were not collected. However, data on height and weight were collected, and the percentiles were numerical increased from baseline. These results suggest that measuring head circumference is not necessary, because for children with cystinosis, the percentile of head circumference increases at a normal rate (Gahl, 2002).

In summary, the clinical reviewer agrees with the Division's comments on November 28, 2017, regarding that the Applicant fulfilled the Procysbi Written Request. The reviewer recommends granting Pediatric Exclusivity to the Applicant.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose, drug abuse potential, withdrawal, and rebound studies were not conducted.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

There was no other postmarketing information submitted.

8.8.2. Expectations on Safety in the Postmarket Setting

There were no new safety concerns.

8.8.3. Additional Safety Issues From Other Disciplines

There were no potential issues regarding drug formulation, delivery, or product quality.

8.9. Integrated Assessment of Safety

The overall safety profile of Procysbi in Study RP103-08 is comparable with that of Studies RP103-03 and RP103-04. The exception is that the former had higher vomiting rate (13/15, 86%) than the later (8/13, 61%) in patients age ≤6 years. The former had one death due to gastroenteritis, vomiting, and hypovolemic shock on treatment Day 17, while the later did not have any deaths.

The most frequently reported (≥10% of subjects) SAEs were gastroenteritis, dehydration, vomiting, and electrolyte imbalance.

Because strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in patients with nephropathic cystinosis, Procysbi improved the estimated GFR by 14% from baseline in RP103-08. This result suggests that despite the treatment related vomiting, the benefit-risk ratio did not change. Vomiting is clinically manageable.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting or other external consultations was held.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling underwent extensive negotiations between the Applicant and FDA. See the final negotiated labeling.

10.2. Nonprescription Drug Labeling

There was no nonprescription drug labeling submitted.

11. Risk Evaluation and Mitigation Strategies (REMS)

REMS was not recommended.

12. Postmarketing Requirements and Commitments

On August 9, 2013, FDA issued a Written Request of "A one-year open-label, PK/PD, Safety and Efficacy study in pediatric patients with nephropathic cystinosis aged birth to <6 years". See Section 8.7.3 Pediatrics and Assessment of Effects on Growth.

There is no new postmarketing requirement.

13. Appendices

13.1. References

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Levtchenko EN, van Dael CM, de Graaf-Hess AC, Wilmer MJ, van den Heuvel LP, van den Heuvel LP, Monnens LA, Blom HJ. Strict systeamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis. Pediatr. Nephrol. 21:110-113, 2006.

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13.2. Financial Disclosure

A total of 5 clinical investigators participated in the covered clinical Study RP103-08 of Procysbi. The covered clinical study is defined in 21 CFR 54.2(e) which is used to establish the effectiveness. No investigators were part- or full-time employees of the Applicant. The Applicant certified the names of the 5 clinical investigators who did not enter any financial agreements with the Applicant (Section 1.3.4.1 Financial Certification of Clinical Investigators).

Table 22: Financial Disclosure of Covered Clinical Study (Name and/or Number): RP103-08

Was a list of clinical investigators provided:	Yes √	No ☐ (Request list from Applicant) N/A
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in Sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	N/A	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided:	N/A	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	N/A	No ☐ (Request explanation from Applicant) N/A

13.3. Individual Patient Height and Weight Z-Scores in Study RP103-08

Table 23: Individual Height and Weight Z-Scores (Study RP103-08)

Patient ID#	Age at Enrollment (years)	Visit	Height		Weight	
			Z-score	Percentile	Z-score	Percentile
01-008	9.03	SCREENING	(b) (4)			
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		STUDY EXIT				
01-009	1.64	SCREENING				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		MONTH 18				
		STUDY EXIT				

(Continued)

Patient ID#	Age at Enrollment (years)	Visit	Height		Weight	
			Z-score	Percentile	Z-score	Percentile
01-010	1.18	DAY 1	(b) (4)			
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		STUDY EXIT				
01-012	2.42	DAY 1				
		WEEK 2				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		STUDY EXIT				

(Continued)

Patient ID#	Age at Enrollment (years)	Visit	Height		Weight	
			Z-score	Percentile	Z-score	Percentile
01-013	1.05	SCREENING	(b) (4)			
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		STUDY EXIT				
21-001	4.53	SCREENING				
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		MONTH 18				
		STUDY EXIT				

(Continued)

Patient ID#	Age at Enrollment (years)	Visit	Height		Weight	
			Z-score	Percentile	Z-score	Percentile
21-002	1.80	SCREENING	(b) (4)			
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		MONTH 18				
		STUDY EXIT				
21-003	1.89	SCREENING				
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		MONTH 18				
		STUDY EXIT				

(Continued)

Patient ID#	Age at Enrollment (years)	Visit	Height		Weight	
			Z-score	Percentile	Z-score	Percentile
21-004	2.58	SCREENING	(b) (4)			
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		MONTH 18				
		STUDY EXIT				
		SCREENING				
21-005	2.33	SCREENING				
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		MONTH 18				
		STUDY EXIT				

(Continued)

Patient ID#	Age at Enrollment (years)	Visit	Height		Weight	
			Z-score	Percentile	Z-score	Percentile
21-006	2.28	SCREENING	(b) (4)			
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		MONTH 18				
		STUDY EXIT				
21-007	3.7	SCREENING				
		DAY 1				
		WEEK 2				
21-008	2.41	SCREENING				
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		MONTH 18				
		STUDY EXIT				

(Continued)

Patient ID#	Age at Enrollment (years)	Visit	Height		Weight	
			Z-score	Percentile	Z-score	Percentile
21-009	3.09	SCREENING	(b) (4)			
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		MONTH 18				
		STUDY EXIT				
21-010	1.04	SCREENING				
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		MONTH 15				
		MONTH 18				
		STUDY EXIT				

(Continued)

Patient ID#	Age at Enrollment (years)	Visit	Height		Weight	
			Z-score	Percentile	Z-score	Percentile
21-011	1.43	SCREENING	(b) (4)			
		DAY 1				
		WEEK 2				
		WEEK 4				
		WEEK 6				
		WEEK 8				
		WEEK 10				
		WEEK 12				
		MONTH 6				
		MONTH 9				
		MONTH 12				
		STUDY EXIT				

From Section 1.11.3 Clinical Information Amendment submitted on October 26, 2017.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEN-YI GAO
12/01/2017

ANIL K RAJPAL
12/01/2017