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APPLICATION NUMBER:

203389Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
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Reviewer Name(s) Carla Epps, MD, MPH
Review Completion Date April 26, 2013

Established Name RP103 (Cysteamine bitartrate)
(Proposed) Trade Name PROCYSBI
Therapeutic Class Cystine depleting agent
Applicant Raptor

Formulation(s) 25 mg & 75 mg oral capsules
Proposed Dosing Regimen Starting dose: 1/4 to 1/6 of
maintenance dose
Maintenance dose:
Age \geq 6 years: 1.3 gram/m²/day (2
divided doses, Q 12 hrs)
Proposed Indication(s) Management of nephropathic
cystinosis
Proposed Intended
Population(s) Children \geq 6 years and adults with
nephropathic cystinosis

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval action for PROCYSBI for the management of nephropathic cystinosis in pediatric patients 6 years and older and in adult patients. I recommend that the pediatric indication be limited to pediatric patients 6 years and older because no efficacy data and safety data were available for pediatric patients under 6 years old. The recommended starting dose is 1/4 to 1/6 of the maintenance dose for PROCYSBI. The recommended maintenance dose for PROCYSBI is 1.3 g/m²/day for patients 6 years and older. Physicians can make dosage adjustments based on achievement and maintenance of the patient's target concentration of WBC cystine. Because values obtained for WBC cystine concentration are protein assay-dependent, the target concentration for an individual patient should be determined by individual analytical laboratories using local methodology and calibration of assays. Patients in clinical trials for PROCYSBI received doses ranging from 0.5 g/m²/day to 2.23g/m²/day.

There is sufficient evidence of safety and efficacy based on the pivotal trial (RP103-03) and its extension (RP103-04) to support an indication in treatment-naïve patients as well as patients previously treated with Cystagon and to provide adequate directions for use. Evidence of safety is based on a database of 72 patients with nephropathic cystinosis, which is an orphan indication. The safety database included 68 patients age 21 years or younger.

1.2 Risk Benefit Assessment

The pivotal trial demonstrated that PROCYSBI is non-inferior to Cystagon in the reduction of WBC cystine levels to a level that is considered to be clinically relevant (WBC cystine level < 1 nmol ½ cystine/mg protein). Evidence of long-term efficacy is based on 16 adult and pediatric patients who have been treated for at least 15 months; only three patients have been treated for at least 19 months. Data from the extension trial indicate that patients maintain clinically meaningful reductions in WBC cystine levels with long-term RP103 treatment.

Evidence of long-term safety is based on 27 adult and pediatric patients who were treated for at least 15 months. Based on the data available for review, PROCYSBI appears to have a similar safety profile to the reference product Cystagon. However, the submission did not include efficacy and safety data for pediatric patients less than 6 years old. Sixteen pediatric patients ages 2 years to less than 6 years old have been enrolled in clinical trials to date. The applicant submitted a Proposed Pediatric Study Request

(b) (4)

(b) (4)

(b) (4)

(b) (4) Therefore, the Division will present a Written
Request to the Pediatric Review Committee (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine surveillance for adverse events is recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The following post-marketing commitment was being negotiated with the applicant at the time of this review:

PMC #1: Include elemental impurities for arsenic, cadmium, lead, and mercury per USP <232> for the drug product specification.

Final Report Submission: June 5, 2013

2 Introduction and Regulatory Background

Nephropathic Cystinosis

Nephropathic cystinosis is an autosomal recessive lysosomal storage disorder characterized by accumulation of the amino acid cystine in almost all cells. It has been found in all ethnic groups and has an estimated prevalence of 1:100,000-200,000.¹ The disorder affects an estimated 500 individuals in the US. It is caused by mutations of the *CTNS* gene which encodes the lysosomal cystine carrier cystinosin. However, the pathogenesis of the disease remains unknown. Classic nephropathic cystinosis (early-onset or infantile) is the most common of three variants of the disease, with onset of disease within the first year of life. Intermediate nephropathic cystinosis (juvenile/late-onset) shares all of the clinical features of classic nephropathic cystinosis, with onset typically after 10 years of age. The third variant, non-nephropathic (adult) cystinosis is characterized by ocular involvement only. Some genotypes are more commonly associated with a particular variant (e.g. truncating *CTNS* mutations and classic disease). However, phenotypic differences have been described between members of the same family.²

Clinical features of the disease include impaired renal function, renal Fanconi syndrome, growth failure, hypophosphatemic rickets, hypothyroidism, and primary hypogonadism in males. Nephropathic cystinosis is the major cause of inherited Fanconi syndrome.³ Presenting features in infants include signs of Fanconi syndrome before age 6 months and growth failure from age six months onward. Onset of corneal involvement may also start within the first year of life and clinical evidence of corneal disease (cystine crystals present on slit lamp examination) is always present by age 16 months. Patients with intermediate cystinosis may have absent or mild Fanconi syndrome and corneal events during childhood. However, progression to end-stage renal disease universally occurs, typically between age 15 and 25 years.

Prior to the development of cystine depleting therapy, renal transplantation was demonstrated to stabilize or prolong renal function and overall survival in nephropathic cystinosis patients.⁴ Cystine crystals do not accumulate in kidney allograft tissue; however, pre-existing renal tubular damage in the host kidney is irreversible. Renal transplantation does not alter the course of non-renal disease.

Current Therapy

The current standard of care for nephropathic cystinosis is treatment with a cystine depleting agent (cysteamine bitartrate) to decrease cellular deposits of cystine, with initiation of treatment as soon as possible after diagnosis. Cystine depletion therapy

1 Nesterova G, Gahl WA, Cystinosis, GeneReviews™- NCBI Bookshelf
<http://www.ncbi.nlm.nih.gov/books/NBK1400/>

2 Wilmer MJ, Schoeber JP et al, Cystinosis: practical tools for diagnosis and treatment, *Pediatr Nephrol* 2011; 26:205-215.

3 Ibid.

4 Almond PS, Matas AJ et al, Renal transplantation for infantile cystinosis: long-term follow-up, *J Pediatr Surg* 1993; 28(2):232-8.

slows progression of both renal and non-renal disease. Therefore, cysteamine is recommended for all nephropathic cystinosis patients, regardless of age or renal transplantation status. Measurement of white blood cell (WBC) cystine levels is used for disease diagnosis and to monitor treatment response. Historically, cystine depletion therapy targeted achievement of WBC cystine levels below 1 nmol ½ cystine/mg protein. However, therapeutic goals for the disease are evolving. In 2005, a group of clinical experts and researchers issued a consensus statement recommending that consideration be given to dosing patients with cysteamine at levels that will achieve near-normal WBC cystine levels (normal= <0.2 nmol ½ cystine/mg protein).⁵

Supportive care for nephropathic cystinosis focuses on management of renal and non-renal disease manifestations. Renal disease management includes treatment of renal Fanconi syndrome (e.g., fluid and electrolyte management, ACE inhibitors to treat proteinuria, etc.) and renal transplantation for patients with end-stage renal disease. Non-renal disease management may include nutritional support, growth hormone and thyroid hormone replacement, carnitine supplementation, and gastrostomy feedings.

Investigational therapies for cystinosis include ophthalmic cysteamine drops (insufficient tissue levels are achieved with oral cysteamine therapy to dissolve corneal cystine deposits). Preclinical investigations include evaluation of bone marrow and hematopoietic stem cell transplantation in a mouse model of cystinosis.⁶

2.1 Product Information

RP103 (cysteamine bitartrate) is an enteric-coated microbead delayed-release capsule. The formulation used in clinical trials was 75 mg capsules.

The proposed indication for RP103 is the management of nephropathic cystinosis in children and adults. The Applicant has proposed dosing for initial treatment and for maintenance treatment. For each of these two dosing regimens, the Applicant proposes two dosing levels (b) (4) for initial treatment and for maintenance treatment, (b) (4). The proposed starting doses are every 12 hours (b) (4). The proposed maintenance doses are (b) (4) divided into two doses every 12 hours (b) (4).

5 Kleta R, Kaskel F et al, First NIH Office of Rare Diseases Conference on Cystinosis: past, present, and future, *Pediatr Nephrol* 2005; 20:452-454.

6 Yeagy BA, Harrison F et al, Kidney preservation by bone marrow cell transplantation in hereditary nephropathy, *Kidney Int* 2011; 79:1198-1206

Reviewer Comments:

The reference product Cystagon, which has an indication for pediatric and adult patients with nephropathic cystinosis, was evaluated in children as young as 5 months old. (b) (4)

However, as discussed in Section 5 of this review, RP103 was not evaluated in children under age 6 years in the pilot study or pivotal trial. A limited number of children under age 6 years have been enrolled to date in a long-term extension trial (RP103-04). (b) (4)

The applicant has submitted a proposed protocol for a pediatric trial in children (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Available Treatments for Proposed Indications

Drug	Formulation	Indication	Dosage
Cystagon (cysteamine bitartrate)	50 mg and 150 mg capsules for oral administration	Management of nephropathic cystinosis in children & adults	Age < 12 years: 1.30 grams/m ² /day Age >12 years: 2 grams/day, (Given in four divided doses)

Cystagon (cysteamine bitartrate)

Cystagon, the reference product for this application, received approval for the management of nephropathic cystinosis in 1994. Warning information for Cystagon includes severe skin rashes, central nervous system symptoms (seizures, lethargy, somnolence, depression, and encephalopathy), and gastrointestinal ulceration and bleeding. Cystagon is contraindicated in patients who are allergic to cysteamine or penicillamine. See Section 2.4 for other adverse reactions.

2.3 Availability of Proposed Active Ingredient in the United States

Cystagon, manufactured by Mylan, is the only product approved in the U.S. for the treatment of nephropathic cystinosis. At the time of this application, there are no drug shortage issues for Cystagon.

2.4 Important Safety Issues With Consideration to Related Drugs

The most frequently reported adverse reactions in clinical trials (reported in > 5% of patients) were vomiting, anorexia, fever, diarrhea, lethargy, and rash. The labeling also notes that patient withdrawals due to adverse reactions appeared to be dose-related, with trial withdrawal occurring more frequently in patients receiving doses at highest labeled dosing (1.95 g/m²/day) compared to patients receiving doses at the lowest labeled dosing (1.3 g/m²/day). Adverse events reported post-marketing included pseudotumor cerebri with papilledema, skin lesions, molluscoid pseudotumors, skin

striae, skin fragility, joint hyperextension, genu valgum, osteopenia, compression fracture, and scoliosis.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- December 11, 2008: PIND was held meeting with the Division. During the PIND meeting, the Division agreed that a 505(b)(2) application would be acceptable for seeking approval. The Division also agreed that white blood cell (WBC) cystine level (measured in nmol $\frac{1}{2}$ cystine/mg protein) was an appropriate primary efficiency endpoint for the pivotal study (RP103-03).
- April 17, 2009: IND 103,694 was opened for pilot study RP-103-01.
- January 28, 2010: EOP2 meeting to discuss the results of pilot study RP103-01. The Division recommended that the Applicant submit a Special Protocol Assessment (SPA) for review prior to initiating Phase 3 trials.
- March 3, 2010: The Applicant submitted a SPA for RP103-03.
- April 16, 2010: The Division issued a No Agreement letter for the SPA based on the proposed study design (non-randomized, open-label design, study eligibility criterion for baseline WBC cystine level, and dosing regimen).
- May 10, 2010: The Applicant submitted a second SPA for RP013-03.
- June 25, 2010: The Division issued another No Agreement letter based on the proposed eligibility criterion for baseline WBC cystine level and the proposed statistical analysis for RP103-03.
- October 25, 2011: Pre-NDA meeting was held with the Division.
- March 30, 2012: The Applicant submitted NDA 203389 application.
- December 19, 2012: The Division issued a Review Extension-Major Amendment letter after receiving a solicited amendment to the CMC portion of the application (dissolution acceptance criteria for the drug product). The major amendment extended the PDUFA date for action on the application to April 30, 2012.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was an electronic submission. Significant CMC and clinical data were missing in the original submission, prompting multiple information requests by the Agency. In addition, the applicant submitted errata to the clinical study reports for RP103-03 and RP103-04 regarding bioanalytical analyses of WBC cystine concentrations (the primary efficacy endpoint in both trials). At the time of this review, the applicant had submitted 29 amendments to the BLA including amendments to efficacy data sets and amended clinical study reports for Studies RP103-03 and RP103-04. [Table 2](#) lists some of the significant amendments to the NDA and the dates of their submission.

Table 2: Substantive Amendments to NDA 203389

NDA Amendment Sequence	Purpose of submission	Date of submission
203389-004	Submission of CMC data regarding proposed dissolution method per Agency request	05/29/12
203389-005	Submission of labeling with format changes per Agency request	06/26/12
203389-006	Submission of CMC data regarding alcohol dose dumping study per Agency request	07/18/12
203389-007	Submission of statistical analyses and SAS programs per Agency request	07/25/12
203389-008	Submission of 120 Day Safety Report	08/07/12
203389-015	Submission of CMC data regarding drug substance specification	10/09/12
203389-016	Submission of clinical and pharmacology datasets per Agency request	10/16/12
203389-018	Submission of 120 Day Safety Report datasets per Agency request	10/26/12
203389-021	Submission of errata to bioanalytical reports affecting statistical analysis of primary endpoint	11/19/12
203389-022	Submission of updated CMC data per Agency request	11/26/12
203389-023	Submission of updated labeling based on data from 120 Day Safety Report	11/30/12
203389-024	Submission of updated CMC data per Agency request	11/30/12
203389-025	Submission of updated bioanalytical reports	12/06/12
203389-026	Submission of updated CMC data per Agency request	12/14/12
203389-027	Submission of updated CMC data per Agency request	12/20/12
203389-029	Submission of updated clinical study report for RP103-03	01/08/13
203389-031	Submission of revised statistical analyses, datasets, and interim clinical study report for RP103-04 per Agency request	01/30/13
203389-032	Submission of CMC data regarding dissolution acceptance criteria per Agency request	02/13/13
203389-033	Submission of updated CMC data regarding drug substance specification per Agency request	02/20/13

Despite the issues with the submission described above, the submission was well organized and of adequate quality to allow comprehensive review of the data. I conducted my review of the clinical data using the amended clinical reports and datasets.

Protocol Amendments

Major amendments to study protocol criteria are summarized below.

RP103-01

There were three amendments to RP103-01:

Amendment 1 (dated May 15, 2009)

- Added individual and overall study stopping criteria
- Added safety ECG assessments
- Adjusted PK and PD sampling times
- Modified eligibility criteria (removed criterion regarding contraception and maximum allowed total daily Cystagon dose)

Amendment 2 (dated June 16, 2009)

- changed the normalized Cystagon dose (allowed doses other than 450 mg) and
- Eliminated the washout period

Amendment 3 (dated August 16, 2009)

- Changed the allowed increase in RP103 dose (changed from up to 100% to up to 200% of Cystagon dose)
- Modified drug administration conditions (allowed administration with acidic liquid and a meal)
- Added assessment of impact of RP103 on use of concomitant gastric acid reduction therapies (i.e., PPIs and/or antacid medications)

RP103-03

The Applicant notes that four amendments were made to RP103-03 to incorporate DGIEP comments and recommendations, including comments made on a Special Protocol Assessment (SPA) that the Applicant submitted in March 2010. The Applicant notes that no patients were enrolled under the initial protocol or under Amendment 1.

Amendment 1 (dated February 21, 2010)

- Updated study endpoints (WBC cystine level; non-inferiority margin of 0.3 tested at 0.025 significance level) and statistical analysis plans (included plan for sample size re-estimation)
- Added collection of PK as well as PD data
- Clarified eligibility criterion regarding trial entry Cystagon dose (i.e., patients must be on stable Cystagon dose that resulted in a clinically meaningful reduction in WBC cystine level)

Amendment 2 (dated May 3, 2010)

- Added a Run-in Period
- Changed trial design to a randomized parallel cross-over trial
- Modified eligibility criteria to limit trial participation to patients with WBC cystine levels <1 nmol $\frac{1}{2}$ cystine/mg protein, specify age and weight restrictions, and to specify parameters for clinically significant changes in renal and liver status
- Updated study objectives, endpoints, and analysis plans

Amendment 3 (dated July 22, 2010)

- Modified eligibility criteria to allow enrollment of patients with WBC cystine levels ≤ 2 nmol $\frac{1}{2}$ cystine/mg protein during the run-in period
- Adjusted of PD sampling times
- Modified patient randomization to stratify patients by baseline WBC cystine levels
- Changed length of run-in period (shortened from 3 to 2 weeks)
- Established minimum sample size of 30 patients
- Modified eligibility criteria to include patients with WBC cystine levels ≤ 2 nmol $\frac{1}{2}$ cystine/mg protein

Amendment 4 (October 22, 2010)

- Provided RP103 starting daily dose (changed from 70% to 80% of daily Cystagon dose) and maximum allowed dose (increased to 100% of daily Cystagon dose) at the end of the run-in period

RP103-04

There were five amendments to the protocol:

Amendment 1 (dated March 11, 2010)

- Modified the clinic visit schedule (schedule changed to monthly visits for at least six months followed by synchronized quarterly visits)
- Provided RP103 starting daily dose (70% of daily Cystagon dose) and maximum allowed dose (100% of daily Cystagon dose) for additional patients enrolled into trial (i.e., patients not entering from RP103-03)
- Removed minimum weight eligibility criterion
- Eliminated one of the exploratory endpoints (gastrointestinal symptoms) from trial
- Changed to use of the self-report PedsQL instrument instead of parent proxy report
- Added safety and PK/PD data reviews during or prior to each study visit

Amendment 2 (dated May 20, 2010)

- Modified eligibility criterion requiring patients to be on a stable Cystagon dose at trial entry (removed language defining stable dose as a dose that results in a “meaningful reduction” in WBC cystine level)
- Clarified liver and renal function eligibility criteria (provided specific cut-off values for liver enzymes and GFR)

- Changed to use of an investigator-administered VAS swallowing difficulty instrument instead of a patient-reported instrument
- Changed PD sampling times
- Clarified definition of meaningful reduction in WBC cystine level (defined as <1 nmol ½ cystine/mg protein)

Amendment 3 (dated August 9, 2010)

- Required that RP103-03 trial be completed and data analyzed prior to opening enrollment to additional patients
- Added stopping criteria that were consistent with RP103-03

Amendment 4 (dated May 2, 2011)

- Modified RP103 dosing to align with dosing modifications made in RP103-03 (starting dose changed from 70% to 80% of daily Cystagon dose and maximum allowed dose increased to 100% of daily Cystagon dose)
- Clarified timing of enrollment and screening schedule for patients not entering from RP103-03
- Modified dose administration recommendations for RP103 (fasting prior to dosing and snack/meal 30-60 minutes after dosing)
- Described a correction factor for total protein used to allow comparison of WBC cystine levels measured by different methods

Amendment 5 (September 27, 2011)

- Provided published results of RP103-03 and bioequivalence trials (RP103-02 and RP103-05)
- Modified study doses (starting daily dose of RP103 changed to 70% of stable baseline and dose increase of up to 100% of stable Cystagon dose allowed)
- Allowed enrollment of patients unable or unwilling to take intact capsules, including patients requiring drug administration via a gastric tube
- Added a Dose Confirmation Period for patients not entering from RP103-03
- Noted a food effect on cysteamine absorption (decreased absorption with a high fat meal)
- Modified drug administration instructions regarding food intake and timing; allowed administration of study drug via gastric tube and/or administration of opened capsules

Reviewer Comments:

The focus of the amendments to RP103-03 was primarily safety monitoring and modifications of PK/PD sampling to allow better characterization of the PK/PD profile.

As noted earlier, the amendments made to RP103-03 were in response to DGIEP comments on a SPA submitted by the applicant (see Special Protocol Assessment-No

Agreement letter dated June 25, 2010 for further details). DGIEP made several recommendations for increasing the robustness of the pivotal clinical trial. The applicant incorporated the following recommendations prior to patient enrollment:

- *Use of a randomized, parallel crossover study design*
- *Run-in period to confirm that patients meet eligibility criterion for WBC cystine level*
- *WBC cystine level of 1 nmol ½ cystine/mg protein as the upper bounds for the non-inferiority margin*
- *Revision of the statistical analysis plan*

The applicant did not agree with another DGIEP recommendation- that the study population be limited to patients that were able to achieve a WBC cystine level < 1 nmol ½ cystine/mg protein, the threshold target cited in current expert consensus guidelines for titration of cysteamine dosing (some treatment centers attempt to achieve near normal WBC cystine levels [normal is < 0.2 nmol ½ cystine/mg protein]). RP103-03 enrollment included stratified enrollment of patients with WBC cystine levels up to 2 nmol ½ cystine/mg protein. Overall, the protocol amendments were adequate to address study design deficiencies identified by the Division and did not adversely impact the interpretability of trial data.

There were no significant changes to the primary efficacy endpoint or to statistical analyses in RP103-04.

3.2 Compliance with Good Clinical Practices

The Applicant states that RP103 clinical trials were conducted in full compliance with the United States (USA) Food and Drug Administration (FDA) regulations applicable to clinical trials (including 45 CFR 46, 21 CFR 50, 21 CFR 56, 21 CFR 312) and International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs) Guidelines and in accordance with the Declaration of Helsinki.

The Division of Scientific Investigations (DSI) was consulted to determine the reliability of data by evaluating US and foreign clinical sites with most enrolled patients for trials RP103-03 and RP103-04. A total of two clinical sites were inspected (see [Table 3](#)). These sites were selected for inspection because of their high enrollment and geographic location (one domestic and one foreign site). The DSI inspector (Khairy Malek, M.D.) reported that no significant regulatory violations were noted and concluded that data from the two sites could be used in support of the NDA.

In addition, due to concerns about the calculation errors for WBC cystine concentration for Study RP103-03, DSI conducted a “for cause” data validation inspection at the bioanalytical site that performed the analyses: (b) (4). (b) (4) also performed analyses at a second site in the (b) (4) however, this site is now closed. DSI reported that no significant regulatory violations were noted. However, the inspectors observed that several testing

methodologies are used to measure protein when determining WBC cystine levels and that the absolute (but not relative) values obtained vary depending upon the methodology used.

Table 3: DSI Site Inspections

Site/Investigator(s)	Protocol ID	Number of Subjects
Site 03 Larry Greenbaum, MD, PhD Emory University School of Medicine 2015 Uppergate Drive NE Atlanta, GA 30322- USA	RP103-03 RP103-04	13 12
Site 06 Patrick Niaudet, MD Centre de Référence des Maladies Rénales Héréditaires de l'Enfant et de l'Adulte Hôpital Necker-Enfants Malades 149 rue de Sèvres 75743 Paris Cedex 15- FRANCE	RP103-03 RP103-04	6 6

Reviewer Comments:

Because the specific testing methodology to measure WBC cystine concentration does not affect the relative values for testing results (i.e., the relative ratio of WBC cystine concentration with RP103 treatment to WBC cystine concentration with Cystagon treatment does not change by methodology), the analysis of trial data was not adversely impacted. However, this issue should be addressed in product labeling. The applicant's proposed labeling and the current labeling for Cystagon both state that dosing should be titrated to achieve a target WBC cystine level of < 1 nmol ½ cystine/mg protein. The labeling for both products should be amended to note that, if WBC cystine levels are used to adjust dosing of cysteamine bitartrate, target concentrations of cystine in WBC should be determined by individual analytical laboratories using local methodology and calibration of protein assays.

3.3 Financial Disclosures

The Applicant stated that no investigators involved in the clinical trials submitted in supported of the application had any financial arrangements with the Applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

RP103 capsules (cysteamine bitartrate delayed-release capsules) are a beaded, enteric-coated, delayed-release formulation of the bitartrate salt of cysteamine (an aminothiol, β -mercaptoethylamine). The microspherized beads are further encapsulated in hard gelatin, and intended for oral administration (whole capsules; sprinkles on food or in liquid). RP103 will be available as 25 mg and 75 mg capsules (expressed as cysteamine free-base). Both 25 mg and 75 mg strength capsules were administered in the pivotal Phase 3 trial (RP103-03) for RP103.

Product quality review

The CMC data were reviewed by the Product Quality Reviewer Jane Chang, Ph.D. and the Biopharmaceutics reviewer Kareen Riviere, Ph.D. (see the CMC and Biopharmaceutics reviews for the complete review of the product data). Dr. Chang identified a number of quality issues in the Product Quality review. One key issue that impacted the review of the NDA was an error in the analyses of the dosage forms of Cystagon and RP103 used in Study RP103-03. A corrected analysis of the dosage forms revealed that the Cystagon dosage forms contained 85% of the stated dose and the RP103 contained ~91% of the stated dose in the phase III clinical trial. The corrected Cystagon and RP103 dosage strength data were reviewed for the clinical pharmacology and clinical reviews. All other quality issues also have been resolved with the following exception:

- Elemental impurities for arsenic, cadmium, lead, and mercury per USP <232> were not included in the drug product specification

The applicant agreed to address this issue as a post-approval commitment with a fulfillment date of June 5, 2013. In addition, the applicant has agreed to submitting the results of an ongoing long-term stability study and to initiating a supplemental stability study.

Dr. Chang also noted that the amount of one of the excipients (Eudragit L 30 D-55) exceeds the maximum for oral tablet/capsule listed in the FDA Inactive Ingredient Search for Approved Drug Products. However, this was not considered to be an issue by the Pharmacology/Toxicology reviewer since the estimated total dose of Eudragit would provide an adequate safety margin based on safety margins derived from toxicity studies conducted by the manufacturer of Eudragit.

Dr. Chang concluded that the applicant had provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, she recommended that the NDA not be approved until labeling issues regarding information on dosage

forms and strengths, dosage and administration, and storage and handling of the drug product were resolved satisfactorily (see [Section 4.1.1](#)).

The Biopharmaceutics reviewer, Kareen Riviere, Ph.D., recommended an action of approval for the application. However, Dr. Riviere noted that the findings of in vitro alcohol induced dose dumping indicated the potential for RP103 delayed-release capsules to release their entire contents in the stomach when co-administered with alcohol. In light of this concern, Dr. Riviere recommended that the results of this study be addressed in labeling information on drug administration (see [Section 4.1.1](#)).

Reviewer Comments:

One of the labeling issues included information on administration of the product through a gastrostomy tube (b) (4). The sponsor did not perform an in vitro study but provided information from Study RP103-04 on administration of the study drug mixed with applesauce through a gastrostomy tube (b) (4) size 12 French and larger. In the earlier trials, the study drug was only administered orally. Dr. Chang determined that the information was acceptable from a CMC perspective to support labeling for administration via a gastrostomy tube (b) (4). In this reviewer's opinion, the information is acceptable to support labeling from a clinical perspective as well.

4.1.1 CMC Labeling Recommendations

CMC recommendations for labeling revisions included the following:

- **Changes to “Highlights”:**
 - Established name should be cysteamine bitartrate (in exception to USP Salt Policy) to provide consistency with Cystagon label
 - Provide route of administration

- **Changes to “Full Prescribing Information”:**
 - Section 2- Dosage and Administration-Provide specific instructions for administration with liquids (b) (4)
 - Section 2-Dosage and Administration (b) (4)
 - Section 3- Dosage Forms and Strengths- Clarify description of dosage form and strength, and identifying characteristics (e.g., capsule color) of the dosage forms

- Section 11- Description- include information on amount of active moiety in dosage form
- Section 16-How Supplied/Storage and Handling- Clarify handling instructions

4.1.2 CMC Action Recommendation

Non-Approval (until agreement upon product labeling)

Reviewer Comments:

The applicant noted that doses of Eudragit L 30 D-55 between 30 and 225 mg/kg/day have been described as potentially related to fibrosing colonopathy in patients with cystic fibrosis (Littlewood 1999) but that animal studies to date have not demonstrated this relationship.

This reviewer agrees with the Product Quality and Biopharmaceutics reviewers' labeling recommendations.

Facility review/inspection

Three facilities are involved in the manufacturing of RP103. The Office of Compliance has made an overall "Acceptable" recommendation for these facilities.

Microbiology product quality

Microbiology product quality considerations do not apply to this application because cysteamine bitartrate is not a biologics product.

Immunogenicity

Immunogenicity considerations do not apply to this application because cysteamine bitartrate is not a biologics product.

4.2 Clinical Microbiology

Clinical microbiology considerations do not apply to this application because cysteamine bitartrate is not an antimicrobial agent.

4.3 Preclinical Pharmacology/Toxicology

The preclinical Pharmacology/Toxicity reviewer for this application was Fang Cai, Ph.D. No new nonclinical studies were conducted by the applicant. The applicant relied upon published data and the Agency's findings from its review of the reference product Cystagon. Dr. Cai recommended an action of approval for the drug product.

Cited nonclinical studies included safety pharmacology studies in mice and rats and a 58-week chronic toxicity study in monkeys. In the safety pharmacology studies, central nervous system effects (decreased motor activity, sedation, and lethargy), gastric and duodenal ulcers, and cardiovascular effects were associated with higher doses of

cysteamine. In the chronic toxicity study in monkeys, the target organs of toxicity in rats and monkeys were the gastrointestinal tract and the liver.

The labeling for Cystagon notes that cysteamine has not been tested for its carcinogenic potential in long-term animal studies. Mutagenicity testing results were negative for the Ames test. Cysteamine produced a negative response in an *in vitro* sister chromatid exchange assay in human lymphocytes but produced a positive response in a similar assay in hamster ovarian cells. In reproductive studies in rats, cysteamine reduced adult fertility and offspring survival at an oral dose of 375 mg/kg/day (2250 mg/m²/day, 1.7 times the recommended human dose). Teratogenic effects (cleft palate, kyphosis, heart ventricular septal defects, microcephaly, and exencephaly) were observed at oral doses of 37.5 to 150 mg/kg/day (~0.2 to 0.7 times the recommended human dose). The labeling also noted a “manifested potential of cysteamine developmental toxicity” in rat lactation studies at an oral dose of 375 mg/kg/day (2,250 mg/m²/day, 1.7 times the recommended human dose).

Dr. Cai concluded that the information from health authorities, U.S. regulations, and toxicity studies submitted by the applicant provide a reasonable assurance of safety for the estimated maximum daily intake of the excipients in RP103.

4.3.1 Pharmacology/Toxicology Labeling Recommendations

- Changes to “Full Prescribing Information”

(b) (4)

4.3.2 Pharmacology/Toxicology Action Recommendation

Approval

Reviewer Comments:

This reviewer agrees with the Pharmacology/Toxicology reviewer’s labeling recommendations.

4.4 Clinical Pharmacology

The applicant conducted three clinical pharmacology studies in healthy volunteers (RP103-02, RP103-05, and RP103-06) and three studies in patients with nephropathic cystinosis (RP103-01, RP103-03, and RP103-04). In addition, the applicant conducted *in vitro* studies to assess for potential drug-drug interactions. The clinical pharmacology data were reviewed by the Clinical Pharmacology reviewer, Kristina Estes, Ph.D. and the Pharmacometrics reviewer Justin Earp, Ph.D. The reviewers determined that the

clinical pharmacology and biopharmaceutics information provided in the submission were acceptable. They recommended an action of approval for the drug product, contingent on the Agency reaching a mutual agreement with the applicant on labeling.

4.4.1 Mechanism of Action

Cysteamine is an aminothiols that participates within lysosomes in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide, thus allowing exit of these products from the lysosome in patients with cystinosis.

4.4.2 Pharmacodynamics

In patients with nephropathic cystinosis, cystine accumulates in tissue cells, including leukocytes (white blood cells). Normal individuals and individuals that are heterozygous for cystinosis have WBC cystine levels of < 0.2 nmol $\frac{1}{2}$ cystine/mg protein and usually < 1 nmol $\frac{1}{2}$ cystine/mg protein, respectively. WBC cystine level was the primary efficacy endpoint in the pivotal trial (RP103-03) and its extension study (RP103-04).

4.4.3 Pharmacokinetics

PK in Healthy Volunteers

In RP103-02, RP103 was administered intact and as a sprinkle under fed conditions. An unexpected food effect was observed and PK parameters could not be accurately estimated due to low plasma concentration of cysteamine. Therefore, the planned bioequivalence analysis was not conducted. The study was amended to retest individuals in a fasted condition; however only 4/18 (22%) individuals completed PK sampling while fasting.

Two studies were conducted to evaluate the bioavailability of RP103 when administered as an intact capsule or as a sprinkle with a small meal (Study RP103-05) or an acidic liquid (Study RP103-06). The results of RP103-05 demonstrated that there was a food effect when RP103 was administered 30 minutes post-dose but no effect at 2 hours. In RP103-06, there did not appear to be any impact on the PK profile when RP103 was administered with an acidic liquid (orange juice). The bioavailability of RP103 appeared to be similar whether administered as an intact capsule or as a sprinkle in both studies.

Similar PK profiles were observed in both studies, with t_{max} approximately 3 to 3.5 hours and $t_{1/2}$ approximately 6 hours. [Table 4](#) summarizes PK parameters for RP103-05 and RP103-06.

Table 4: Mean (SD) Plasma Cysteamine Pharmacokinetic Parameters in Healthy Volunteers Following a Single 600 mg Dose of RP103

Pharmacokinetic Parameter	RP103-05		RP103-06	
	Crossover (N=19)		Crossover (N=19)	
	Opened Capsules	Intact Capsules	Opened Capsules	Intact Capsules
AUC _(0-t) (hr•ng/mL)	7965 (1984)	7795 (1779)	6795 (1868)	6868 (1695)
AUC _(0-inf) (hr•ng/mL)	8197 (2049)	(8039 (1848)	7001 (1918)	7087 (1757)
C _{max} (ng/ml)	2316 (718)	2268 (576)	2074 (615)	2157 (415)
T _{max} (hr) ^a	3.00 (1.50 – 6.00)	3.00 (2.00 – 4.00)	3.50 (1.00 – 4.00)	3.5 (2.00 – 4.00)
T _½ (hr)	6.06 (0.970)	6.08 (0.840)	5.78 (0.671)	5.86 (0.817)

^aMedian (range) SD=standard deviation; hr=hour

Source: RP103-05 Clinical Study Report, Table 13

PK/PD in Patients with Nephropathic Cystinosis

The PK/PD profile of RP103 was evaluated in patients with nephropathic cystinosis in 3 clinical trials (RP03-01, RP103-03, and RP103-04). Interpretation of PK data from the pilot study (RP103-01) is limited due to the small number of patients enrolled and the wide PK variability between patients observed in the trial. However, the PK/PD data from Studies RP103-03 and RP103-04 were adequate to characterize the PK/PD profile of RP103. [Table 5](#) summarizes AUC and C_{max} values for RP103 and Cystagon in patients with nephropathic cystinosis enrolled in the pivotal trial (RP103-03). The absorption of cysteamine was slower following RP103 administration compared to absorption following Cystagon administration, with an observed median t_{max} of 3 hours and 1 hour, respectively. The observed mean values for C_{max} and AUC_{0-t} were similar for the two products.

Table 5: Comparison of Cystagon and RP103 PK Parameters in Patients with Nephropathic Cystinosis (RP103-03 Per Protocol Population)

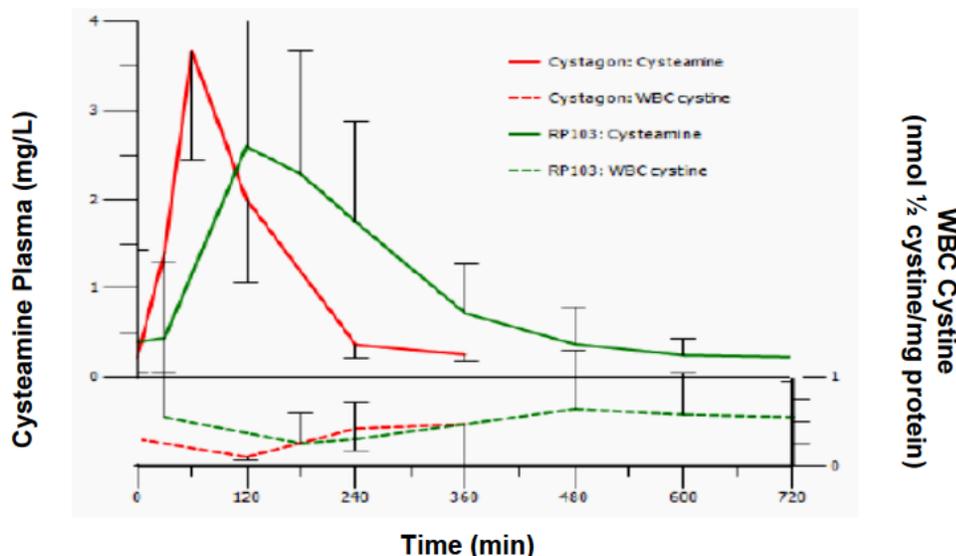
Parameter/ Treatment	N	LS Means ³	Difference in LS Means (RP103- Cystagon [®])	95% CI of Ratio (RP103- Cystagon [®])	Intra-subject CV%
AUC _(0-t) (min*mg/L) Cystagon ^{®1} RP103 ²	39 37	5.76 6.47	0.72	1.75 to 2.39	34.19
AUC _(0-∞) (min*mg/L) Cystagon [®] RP103	39 37	5.85 6.56	0.71	1.76 to 2.36	31.86
C _{max} (mg/L) Cystagon [®] RP103	39 37	0.83 1.16	0.33	1.17 to 1.67	39.92

LS=least squares; CI=confidence interval; CV=coefficient of variation
¹ AUC_(0-t) for Cystagon[®] was calculated based on cysteamine blood levels at each timepoint up to 6 hours post dosing on Day 7 of Week 6 or Week 9.

Source: RP103-03 Final Clinical Study Report (Amended) dated December 26, 2012, Table 9

[Figure 1](#) shows the relationship between the mean plasma cysteamine exposure and the corresponding mean WBC cystine level post-dose for Cystagon and RP103 for RP103-03 patients. As discussed in Section 5, dosing was not fixed but was based on the patients' prior dose of Cystagon. Following RP103 administration, mean WBC cystine levels remained below 1 nmol ½ cystine/mg protein during the 12-hour dosing interval. Mean WBC cystine values were observed to decline following the pharmacokinetics of the immediate-release or delayed-release cysteamine products, with minimum WBC cystine levels occurring shortly after the plasma cysteamine C_{max}. A more rapid decline in WBC cystine levels and a more rapid return to baseline levels was observed post-dose with Cystagon compared to RP103.

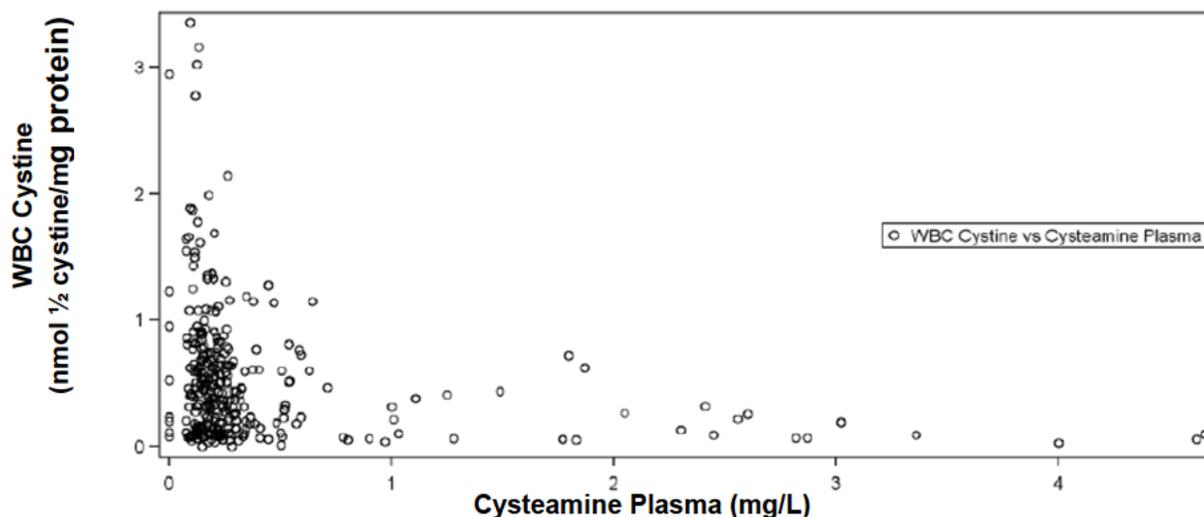
Figure 1: RP103-03: PK/PD Model of WBC Cystine Level (nmol $\frac{1}{2}$ cystine/mg protein) vs. Cysteamine Plasma Concentrations (mg/L)*



*PK/PD Model: Two Compartment Population PK Model; Inhibitory T_{max} PD
Source: RP103-03 Amended Study Report (dated December 26, 2012), Figure 3

A similar PK/PD relationship was observed in RP103-04. Plasma cysteamine levels between 0.1 mg/l and 0.5 m/L correlated well with maintenance of serum WBC cystine levels below 1 nmol $\frac{1}{2}$ cystine/mg protein with a 12-hour dosing interval (see [Figure 2](#)).

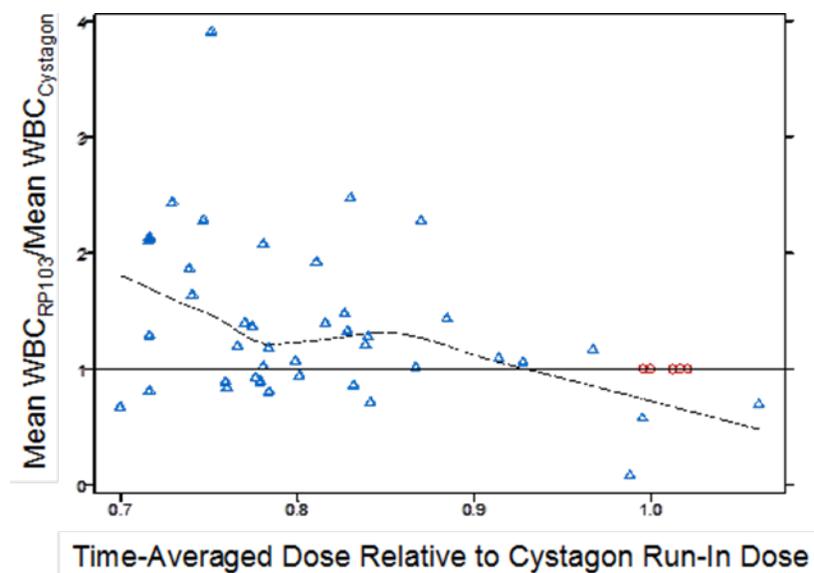
Figure 2: RP103-04: WBC Cystine Level (nmol $\frac{1}{2}$ cystine/mg protein) vs. Cysteamine Plasma Concentrations (mg/L) (PK/PD Population)



Source: RP103-04 Amended Study Report (dated January 10, 2013), Figure 1

The Pharmacometrics reviewer, Justin Earp, PH.D., performed a dose-response analysis of results from RP103-03 evaluate the appropriate dose conversion for RP103. The analysis compared time-averaged dose of RP103 relative to the Cystagon run-in dose (see [Figure 3](#)). The analysis indicated that patients administered a lower dose of cysteamine (i.e., 70-80% of the prior Cystagon dose) with RP103 had higher WBC cystine values. In addition, Dr. Earp noted that most of the patients required a dose increase and that the median RP103 to Cystagon dose ratio for patients who completed the trial (n=41) was 0.91 (95% CI= 0.72, 1.0). Dr. Earp analyzed Cystagon and RP103 doses by patient age (<12 years vs. ≥12 years), weight (< 110 pounds vs. ≥100 pounds), and patient age and weight (age <12 years and/or weight <110 pounds vs. ≥12 years and ≥100 pounds). His analyses indicated that dosing increases for age or weight did not appear to be necessary (see [Table 6](#)).

Figure 3: Relative WBC Cystine Level after RP103 to WBC Cystine Level after Cystagon



△ =patients receiving RP103 ○=patients receiving Cystagon; each point represents data for 1 patient

Source: Pharmacometrics review for NDA 203389

Clinical Review
 Carla Epps, MD, MPH
 NDA 203-389
 Procysbi (cysteamine bitartrate)

Table 6: Median Doses (95% CI) Administered in Study RP103-03 by Patient Age, Patient Weight, and Patient Age and Weight*

Dose Metric/ Demographic	Age < 12	Age ≥12	BW <110	BW ≥110	Age < 12 &/OR BW < 110	Age ≥12 and BW ≥ 110
Baseline Run-In Cystagon	1418 (921, 1770)	1244 (811, 1890)	1356 (864, 1870)	1216 (1040, 1500)	1356 (864, 1870)	1216 (1040, 1500)
Time-Averaged Cystagon	1418 (933, 1770)	1244 (811, 1890)	1356 (864, 1870)	1214 (1060, 1500)	1356 (864, 1870)	1214 (1060, 1500)
Time-Averaged RP103	1107 (851, 1480)	952 (590, 1630)	1100 (676, 1540)	953 (861, 1170)	1100 (676, 1540)	953 (861, 1170)
Ending RP103	1167 (898, 1670)	1101 (265, 1720)	1148 (441, 1770)	1084 (917, 1370)	1148 (441, 1770)	1084 (917, 1370)

*Dose unit=mg/m²/day

Source: Pharmacometrics review for NDA 203389

Based on the results of the dose-response analysis and the lack of safety signals that suggest a need to reduce doses for RP103, Dr. Earp recommended that the starting dose for RP13 be equal to the starting dose (based on body surface area) for Cystagon. He also noted that trial results corroborated prior Agency clinical trial simulation results that indicated that dose increases of 25% would be sufficient to improve efficacy. Dr. Earp recommended revisions to the applicant's proposed labeling regarding dosage, including starting dose, maintenance dose, and dose for patients transferring from Cystagon (see recommendations for labeling revisions below).

4.4.4 Metabolism and transporter studies

The applicant conducted the following in vitro studies to characterize the metabolism of RP103: metabolic stability in human liver microsomes, MAO reaction phenotyping, cytochrome P450 induction (multiple systems), cytochrome P450 induction, P-gp affinity, and affinity for transporter uptake. Testing results indicated that multiple CYP enzymes contribute to the metabolism of RP103 (with the exception of 3A4 and 2D6) but RP103 does not appear to be an inhibitor of CYP enzymes. The results also indicated that RP103 is likely an inducer of CYP1A2 or CYP3A4, and possibly CYP2B6. The results of transporter affinity testing suggest that RP103 is a substrate of P-glycoprotein (P-gp) and Organic Cation Transporter2 (OCT2) but not breast cancer resistance protein (BCRP); RP103 is not an inhibitor of any of these transporters. RP103 is not a substrate of MAO. The applicant noted that RP103 potentially may interact with other OCT2 substrates, including gastric acid-reducing medications commonly used by patients with nephropathic cystinosis. The safety issues of potential drug-drug interactions are discussed in [Section 7.2.5](#) and [Section 7.5.5](#).

4.4.5 Clinical Pharmacology Labeling Recommendations

Clinical Pharmacology recommendations for labeling revisions included the following:

- **Changes to “Highlights”:** Revise dosage information as follows:
 - Starting dose: (b) (4)
 - Maintenance dose: starting maintenance dose of 1.3 g/m²/day
 - Patients transferring from immediate release cysteamine bitartrate capsules: total daily dose of RP103 equal to previous total daily dose of cysteamine

- **Changes to “Full Prescribing Information”:**
 - Section 2- Dosage and administration- Revise dosage information as follows:
 - Starting dose: (b) (4)
 - Maintenance dose: starting maintenance dose of 1.3 g/m²/day
 - Patients transferring from immediate release cysteamine bitartrate capsules: total daily dose of RP103 equal to previous total daily dose of cysteamine

4.4.6 Clinical Pharmacology Action Recommendation

Approval (pending agreement upon product labeling)

Reviewer Comments:

This reviewer agrees with the Clinical Pharmacology labeling recommendations for the starting dose and for dosing for patients transferring from Cystagon.

5 Sources of Clinical Data

The Applicant submitted data on the following studies for review: RP103-01, RP103-02, RP103-03, RP103-04, and RP103-05. Data included completed study reports for RP103-01 (pilot study), RP103-03 (pivotal trial) and RP103-02, RP103-05 and RP103-06 (bioequivalence studies), and an interim study report for RP103-04 (extension study for RP103-03). The RP103-04 interim report included efficacy and safety analysis datasets for 48/60 patients who were enrolled into the study prior to the data cut-off date for the initial application submission. In addition, the applicant submitted a 120-day Safety Report with updated safety data for RP103-04. The RP103-04 safety update included top-line safety data for 12/60 RP103-04 patients who enrolled into the study after the submission data cut-off date. As noted earlier, the applicant reanalyzed efficacy data for RP103-03 and RP103-04 using the recalculated WBC cystine values and submitted amended clinical reports for these studies on January 30, 2013). Safety data are reviewed in [Section 7](#).

I also completed a literature review (See [Section 9.1](#)).

5.1 Tables of Studies/Clinical Trials

The clinical development program for RP103 consists of six clinical trials, including three bioequivalence studies in healthy volunteers (RP103-02, RP103-05, and RP103-06), a pilot study in patients with nephropathic cystinosis (RP103-01), and the pivotal trial (RP103-03) and its long-term extension (RP103-04). The program includes a phase 1 trial (PB-01-2005) and a treatment protocol (PB-06-004). At the time of this review, all studies and clinical trials had been completed, with the exception of RP103-04 which is ongoing. Sixty patients were enrolled in the extension study at the time of submission of this application, including 58 patients 21 years old or younger. See [Table 7](#) for a list of RP103 clinical trials.

Table 7: Table of RP103 Studies & Clinical Trials

Study ID Phase	Study Design	Planned/Actual/Completed	Drug Dose Route of Administration	Study Objective	Study population	Treatment Duration	Status
Pilot Study							
RP103-01 1/2	Single center, single dose, open label, nonrandomized	10/9/9	RP103 450 mg normalized single dose vs. Cystagon 450 mg normalized single dose; Oral (capsules)	PK, Tolerability	Patients with nephropathic cystinosis	Single dose	Completed
Bioequivalence Studies							
RP103-02 1	Single site, randomized, crossover, fed	38/18/17	RP103 600 mg single dose Intact vs. opened capsules mixed with food	BE (intact vs. opened capsules)	Healthy volunteers	3 weeks	Completed
RP103-05 1	Single site, randomized, crossover, fasted	40/20/17	RP103 600 mg single dose Intact vs. opened capsules mixed with food; 30 min & 2 hour meal delay	BE (intact vs. opened capsules; meal delay)	Healthy volunteers	2 weeks	Completed
RP103-06 1	Single site, randomized, crossover, fasted	20/20/19	RP103 600 mg single dose Intact capsules administered with orange juice vs. capsule contents mixed with food	BE (intact vs. opened capsules)	Healthy volunteers	2 weeks	Completed
Clinical Trials							
RP103-03 2/3	Multi-center, randomized, crossover	36/43/41	RP103 Q12H vs. Cystagon Q6H; Oral (capsules)	Efficacy & Safety	Patients with nephropathic cystinosis	9 weeks	Completed
RP103-04 3	Multi-center, long-term, open label	60/60/0	RP103 Q12H; Oral (capsules)	Long-term Safety	Patients with nephropathic cystinosis	Up to 24 months	Ongoing

Source: Applicant's submission

5.2 Review Strategy

Due to differences in eligibility and study dosing criteria, efficacy data from RP103-01 were not integrated with results from RP103-03 and RP103-04. The bioequivalence studies (PR103-02, PR103-05, and RP103-06) were reviewed by the Clinical Pharmacology reviewer, Kristine Estes, Ph.D. (see her review for a detailed description of these studies). The safety data for all RP103 trials are reviewed in [Section 7](#).

5.3 Discussion of Individual Studies/Clinical Trials

RP103-01 (Pilot study)

5.3.1 General Design and Objectives

RP103-01 was a Phase 1/2 single site, single dose, open-label, crossover study to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) profile, safety and tolerability of RP103 ((cysteamine bitartrate delayed release capsules) compared to Cystagon in patients with nephropathic cystinosis. The target enrollment for the trial was six patients; nine patients were actually enrolled.

Nephropathic cystinosis patients who were able to swallow study medication, who were on stable Cystagon therapy (defined as no change in Cystagon dose for at least 21 days prior to study entry) and who were deemed healthy enough to participate by the investigator were eligible for the trial (specific eligibility criteria are listed below in Sections B and C). Study endpoints included safety, PK, and PD (WBC cystine level) parameters. The trial period was from May to July 2009.

There were three amendments of the protocol during the course of the trial. As discussed in Section 3.1, major amendments included addition of individual and overall study stopping criteria, addition of safety assessments, adjustments of the PK/PD sampling schedule, and changes in study dosing and conditions of administration.

5.3.2 Inclusion Criteria

- Male and female nephropathic cystinosis patients on stable Cystagon therapy (i.e., no change in Cystagon dose for at least 21 days prior to study entry)
- Able to swallow intact Cystagon capsule
- WBC cystine level <1 nmol ½ cystine/mg protein (trough level) within last 60 days prior to screening
- No clinically significant change from normal in liver functions tests (i.e., ALT, AST, alkaline phosphatase, and bilirubin [total and direct]) or renal function as determined by the investigator within 2 months of study entry
- Use of an acceptable form of contraception (sexually active female patients of childbearing potential only)

5.3.3 Exclusion Criteria

- Patients receiving less than 450 mg/dose of Cystagon or if study dosing of 450 mg/dose of Cystagon X 2 in a 24-hour period would exceed 1.3 grams/m²/day of Cystagon
- Patients weighing < 22.5 kg with a total daily Cystagon dose of \geq 1800 mg
- Patients anticipated not to tolerate the planned study dose based on their prior Cystagon steady state dosing requirements
- History of current or recent (within 90 days prior to screening) Helicobacter pylori infection
- Active inflammatory bowel disease or history of small bowel resection, cardiac disease (within 90 days of screening), active bleeding disorder (within 90 days of screening), history of malignant disease (within past 2 years)
- Patients who became renal transplant candidates within 3 months of screening or post-renal transplant patients
- Allergy to hypersensitivity to cysteamine and penicillamine
- Pregnant (or planning to become pregnant) or lactating female patients

5.3.4 Endpoints

As noted earlier, safety and PK/PD were the primary endpoints for this trial. Safety assessments included adverse events (AEs), physical examination, vital signs, clinical laboratory assessments (hematology, chemistry, and urinalysis), electrocardiograms (ECGs), and Gastrointestinal Symptoms Rating Scale scores. PK measurements included C_{max} , T_{max} , $t_{1/2}$, AUC, and K_{el} . Other endpoints included use of concomitant gastric acid reduction therapies (i.e., proton pump inhibitors and/or antacid medications).

5.3.5 Treatment

This trial was comprised of a screening period (Day -1) and two treatment periods (Day1 and Day2), an end-of-study visit (Day 3), and a follow-up telephone interview (Day 10). Initially, the screening period and first treatment period were separated by a washout period (Day 0) of 18 to 24 hours. This washout period was eliminated after preliminary PK/PD data from the first 3 enrolled patients demonstrated that WBC cystine levels increased rapidly at the end of the 6-hour Cystagon dosing interval. Subsequently, all assessments scheduled to be performed during the washout period were performed prior to patient dosing during the first treatment period.

During screening, a medical history was obtained to ensure that patients met eligibility criteria. Screening assessments included physical examinations including height and weight, vital signs, concomitant medications, electrocardiogram (ECG), laboratory assessments (chemistry, hematology, and urinalysis), pregnancy screening, screening for liver diseases (HIV and viral hepatitis screening, fasting copper and ceruloplasmin

levels), and AEs. Prior to drug administration in the first treatment period, patient assessments included Gastrointestinal Symptoms Rating Scale scores, food and liquid intake monitoring, an AE Checklist inquiry, AEs, and concomitant medications. In addition, PK and PD samples were obtained.

Assessment during the two treatment periods included vital signs, laboratory assessments (chemistry, hematology, and urinalysis), Gastrointestinal Symptoms Rating Scale scores, food and liquid intake monitoring, AE Checklist inquiries, AEs, concomitant medications, and PK/PD sampling. During the end-of-study visit (Day 3), assessments included physical examinations, vital signs, concomitant medications, ECG, GSRS, laboratory assessments (chemistry, hematology, and urinalysis), AE Checklist inquiry, and AEs. Adverse events were collected during the Day 10 follow-up telephone interview. [Table 8](#) details the schedule of assessments for RP103-01.

Table 8: RP103-01 Schedule of Assessments

Procedure	Screening	Washout	Period 1	Period 2	End-of-Study Visit	Follow-up
	Days					
	-1	0	1	2	3	10 (+) 2
Informed Consent/ Medical History	X					
Height, BMI, BSA	X					
Physical Examination	X				X	
Vital signs	X		X	X	X	
Laboratory tests	X	X	X	X	X	
Urinalysis	X		X	X	X	
Urine pregnancy test (females)	X					
Liver diseases screen*	X					
Safety electrocardiogram	X				X	
GSRS		X	X	X	X	
Food/liquid intake monitoring	X	X	X	X		
AE Checklist inquiry		X	X	X	X	
AE monitoring	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	
Cystagon administration	X	X			X	
RP103 administration			X	X		
Plasma cysteamine samples		X	X	X		
WBC cystine samples		X	X	X		
Phone interview						X

AE=adverse event; BMI=body mass index; BSA= body surface area; GSRS= Gastrointestinal Symptoms Rating Scale

*Liver diseases screen= HIV & viral hepatitis screen, copper, ceruloplasmin levels)

Source: Source: RP103-01 Study Protocol dated August 16, 2009, Appendix 14.1

5.3.6 Study Drug Dosing and Administration

The initial protocol specified a dose of 450 mg of Cystagon or RP103 during the two treatment periods. However, as noted earlier, the protocol was amended to allow other study doses and individual patient dosing varied from 300 mg to 700 mg (2 patients received 300 mg, 5 patients received 450 mg, and 2 patients received 700 mg), corresponding to doses of 0.6 to 1.2 g/m²/day. In addition, the protocol was amended to allow administration of the drug with juice or food, based on results from bioequivalence studies that demonstrated bioequivalence when RP103 was administered with acidic liquids or appropriately timed meals (up to 30 minutes post-dose). The study drug formulations used in the trial were Cystagon 50 mg and 150 mg capsules, and RP103 75 mg capsules.⁷

5.3.7 Concomitant Medications

Patients were prohibited from taking herbal supplements capable of inducing hepatic enzyme metabolism or transport (e.g., St. John's Wort) within 30 days of screening or during the trial. There were no restrictions on the use of other concomitant medications during the trial.

5.3.8 Prohibited Medications

Illegal drug use and alcohol use were prohibited during the study

5.3.9 Safety Considerations/Monitoring

Safety was assessed by adverse events (AEs) and serious adverse events (SAEs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, vital signs, and ECGs.

Safety results were reviewed by the trial investigator. Safety-related criteria for withdrawal of an individual patient included development of an illness or change in clinical status that precluded further treatment or development of an unacceptable AE. The protocol did not provide a list of specific AEs that would be considered unacceptable.

5.3.10 Statistical Analysis Plan

The applicant provided descriptive statistics for the PK/PD and safety data analyses. The safety population included all patients who had received at least 1 dose of study

⁷ In a SPA Resubmission submitted on May 12, 2010, the applicant stated that the largest capsule sizes for Cystagon and RP103 that would be used in clinical trials would be size 0 and noted that size 0 capsules were the largest size capsules that young children would be able to swallow, particularly young child who had swallowing difficulties due to their underlying disease.

drug. The PK and PD analysis populations included all patients who had evaluable PK or PD data.

Determination of Sample Size

The applicant notes that the trial sample size was based on feasibility rather than statistical considerations.

5.3.11 Patient Disposition

All 9 patients (7 boys and 2 girls) that enrolled in the trial completed treatment.

5.3.12 Protocol Violations and Deviations

Two patients were granted exemptions from trial eligibility criteria, including one patient exempted from the criterion requiring patients to be on a stable dose of Cystagon, and one patient exempted from the criterion that excluded patients whose planned study dose would exceed the patient's tolerability of cysteamine. There were 8 minor protocol deviations, including PK samples not collected for 4 patients, and errors in study drug administration (e.g., administered with large meal) reported for 4 patients.

5.3.13 Review of RP103-01 Study Results

A. Demographics

As noted earlier, all patients were required to have baseline normal renal and liver function to be eligible for trial participation. The patients' mean age and weight were 12.8 years (range 7 to 24 years) and 36.8 kg (range 21 to 50.6 kg), respectively (see [Table 9](#)). The mean daily Cystagon dose at screening was 1.8 g/m²/day. The mean baseline WBC cystine level was 0.4 nmol ½ cystine/mg protein; all patients had a baseline WBC cystine level <1 nmol ½ cystine/mg protein.

Table 9: RP103-01 Patient Baseline Characteristics and Cystagon Dosing

Patient	Race	Gender	Age (years)	Weight (kg)	BSA	Cystagon dose (mg/day)	Cystagon dose (g/m ² /day)	WBC cystine level (nmol ½ cystine/mg protein)
1	W	M	13	41.2	1.3	2800 (700 QID)	2.15	0.52
2	W	M	11	35.8	1.2	1400 (350 QID)	1.16	0.32
3	W	M	11	42.2	1.3	2400 (600 QID)	1.85	0.56
4	W	F	13	31	1.1	1800 (450 QID)	1.64	0.33
5	W	M	7	21	0.81	1800 (450 QID)	2.22	0.26
6	W	M	14	40.9	1.3	3000 (750 QID)	2.31	0.36
7	W	F	24	42.2	1.3	3000 (750 QID)	2.31	0.3
8	B	M	9	26.6	1	1400 (350 QID)	1.4	0.55
9	W	M	13	50.6	1.4	1800 (450 QID)	1.29	0.44
Mean			12.8	36.8	1.2	2156	1.81	0.40

Source: Final Report: PK/PD and Safety Summary for Study RP103-01

B. Review of Efficacy

Efficacy Summary

Due to the limited number of patients in the pilot study and the wide inter-patient variability in PK parameters observed in the trial, interpretation of the data is limited. However, the WBC cystine response to oral cysteamine administration appeared to be similar with RP103 and Cystagon, with minimum WBC cystine levels corresponding to C_{max} for both products. The applicant determined a starting dose of RP103 for the pivotal trial using an inhibitory effect sigmoid E_{max} model for pooled PK/PD data for Cystagon and RP103. Based on the applicant's modeling data, the predicted daily dose of RP103 that would reduce WBC cystine levels below 1 nmol ½ cystine/mg protein was 70% of the daily dose of Cystagon. However, the Agency performed PK/PD modeling and clinical trial simulation that indicated that a 25% higher dose (i.e., 87.5 % of the total daily Cystagon dose) would result in more patients achieving a WBC cystine target of <1 nmol ½ cystine/mg protein without exceeding the C_{max} for Cystagon. As discussed earlier in [Section 4.4.3](#), PK data from Study RP103-04 corroborated these trial simulation results.

1. PK Analysis

Following administration of a 450 mg normalized dose, the mean C_{max}, AUC_{0-6h} and AUC_{0-12h} values (calculated directly from RP103 data and from doubling the AUC_{0-6h}

value for Cystagon), were lower for RP103 (C_{max} 27.70 ± 14.99 $\mu\text{mol/L/mg}$; AUC_{0-6h} 89.6 ± 45.8 $\mu\text{mol}\cdot\text{h/L}$; AUC_{0-12h} 118.2 ± 54.6 $\mu\text{mol}\cdot\text{h/L}$) compared to Cystagon (C_{max} 37.72 ± 12.10 $\mu\text{mol/L/mg}$; AUC_{0-6h} 105.9 ± 62.3 $\mu\text{mol}\cdot\text{h/L}$; AUC_{0-12h} 211.9 ± 124.6 $\mu\text{mol}\cdot\text{h/L}$). However, the mean normalized dose AUC_{∞} was higher for RP103 (146.7 ± 69.2 $\mu\text{mol}\cdot\text{h/L}$) compared to Cystagon (118 ± 66.6 $\mu\text{mol}\cdot\text{h/L}$). The applicant attributed this finding to the apparent longer half-life of RP103 compared to Cystagon (5.85 ± 2.89 hours and 1.90 ± 0.58 hours, respectively). The mean T_{max} values for RP103 and Cystagon were 2.78 ± 1.56 hours and 1.22 ± 0.51 hours. The applicant noted that although intra-patient variability was very low, inter-patient variability was high in the study due to inter-patient differences in absorption and elimination of cysteamine. [Table 10](#) summarizes mean PK values for Cystagon and RP103 following a 450 mg normalized dose.

Table 10: RP103-01 PK Parameters of Cysteamine Following Oral Administration of Cystagon and RP103 (450 mg Normalized Dose)

PK Parameter Mean (SD)	Cystagon	RP103
C_{max}/Dose ($\mu\text{mol/L/mg}$)	37.72 (12.10)	27.70 (14.99)
T_{max} (h)	1.22 (0.51)	2.78 (1.56)
$t_{1/2}$ (h)	1.9 (0.58)	5.85 (2.89)
AUC_{∞} ($\mu\text{mol}\cdot\text{h/L}$)	118 (66.6)	146.7 (69.2)
AUC_{0-6h} ($\mu\text{mol}\cdot\text{h/L}$)	105.9 (62.3)	89.6 (45.8)
AUC_{0-12h} ($\mu\text{mol}\cdot\text{h/L}$)	211.9 (124.6)	118.2 (54.6)

SD= standard deviation

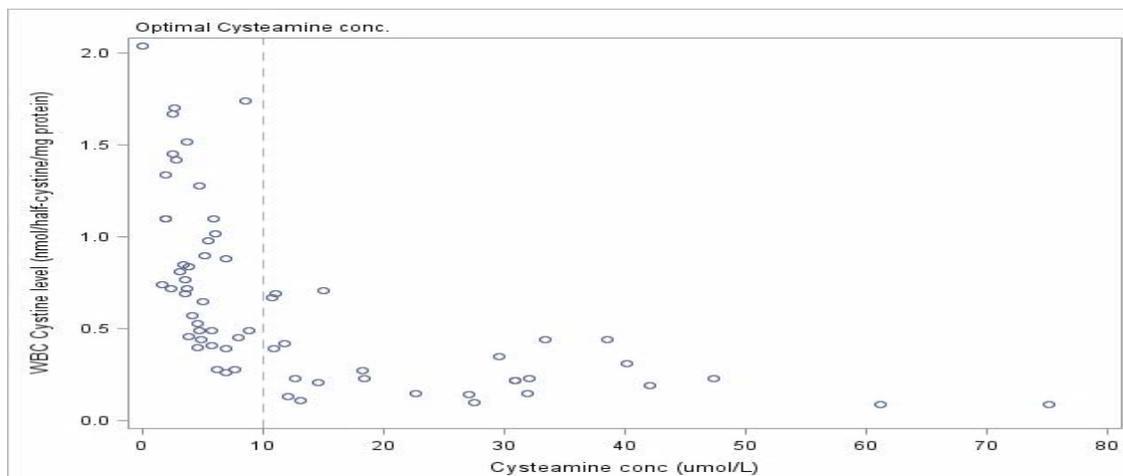
Source: Final Report: PK/PD and Safety Summary for Study RP103-01 (dated February 9, 2010), Table 4

2. PK/PD Relationship

The observed WBC cystine response to cysteamine plasma concentrations appeared to be the same for RP103 and Cystagon. Maximum WBC cystine response appeared to be achieved at plasma cysteamine levels of ~10 to 15 $\mu\text{mol/L}$ (see [Figure 4](#)).

The applicant also pooled RP103 and Cystagon data and modeled (using an inhibitory effect sigmoid E_{max} model) the relationship between the cysteamine concentration and WBC cystine level. The calculated E_{50} was 2.57 nmol/L cysteamine for a maximum decrease in WBC cystine to 0.058 nmol $\frac{1}{2}$ cystine/mg protein from an initial value of 2.015 nmol $\frac{1}{2}$ cystine/mg protein.

Figure 4: RP103-01: Individual Plasma Cysteamine Concentrations ($\mu\text{mol/L}$) vs. WBC Cystine Levels ($\text{nmol } \frac{1}{2} \text{ cystine/mg protein}$)



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Source: Final Report: PK/PD and Safety Summary for Study RP103-01, Figure 12

Based on a regression analysis of the dose-normalized $\text{AUC}_{0-12\text{h}}$ for RP103 versus Cystagon, the applicant determined that a single RP103 dose 1.4 times the amount of a single dose of Cystagon would result in an equivalent exposure of cysteamine over a 12 hour dosing interval. This dosing ratio corresponded to a total daily RP103 dose that is 70% of the total daily Cystagon dose. However, the Agency performed PK/PD modeling and clinical trial simulation that indicated that a 25% higher dose (i.e., 87.5 % of the total daily Cystagon dose) would result in more patients achieving a WBC cystine target of $<1 \text{ nmol } \frac{1}{2} \text{ cystine/mg protein}$ without exceeding the C_{max} for Cystagon (see the Clinical Pharmacology consult [dated May 3, 2010 and entered under IND 103,694] by Pei Fan Bai, Ph.D. and Christine Garnett, Pharm.D. for further details).

RP103-02, RP103-05, RP103-06 (Bioequivalence studies)

See [Section 4](#) for a discussion of clinical pharmacology data for these trials. Safety data for these trials are reviewed in [Section 7](#).

RP103-03 (Pivotal trial)

5.3.14 General Design and Objectives

This was a 9-week, open-label, multicenter, randomized, cross-over, pharmacokinetic (PK) and pharmacodynamics (PD), non-inferiority trial designed to evaluate the safety and efficacy of RP103 (cysteamine bitartrate delayed release capsules) compared to Cystagon in patients with nephropathic cystinosis.

Nephropathic cystinosis patients ages 6 years and older who were on a stable dose of Cystagon (defined as a dose sufficient to maintain a WBC cystine level at ≤ 2 nmol $\frac{1}{2}$ cystine/mg protein) were eligible for the trial. The primary efficacy endpoint was a non-inferiority comparison of the depletion of steady-state cysteamine trough WBC cystine levels after treatment with Cystagon and RP103. Additional efficacy endpoints assessed included quality of life and visual analog score (VAS) for difficulty swallowing due to pain. This trial was conducted in nine sites in three countries: France, Netherlands, and United States. The trial period was from June 23, 2010 to June 3, 2011.

There were four amendments of the protocol during the course of the trial. As discussed in [Section 3.1](#), the applicant made multiple amendments to the protocol to address study design issues identified by the Division during its review of the applicant's proposed SPA. These amendments included a change in trial design to a randomized parallel crossover design, addition of a run-in period to establish that patients were on a stable Cystagon regimen, changes in the WBC cystine eligibility criterion, and modification of the statistical analysis plan, and changes in study dosing.

5.3.15 Inclusion Criteria

- Male and female nephropathic cystinosis patients on a stable Cystagon regime (i.e., able to maintain WBC cystine level ≤ 2 nmol $\frac{1}{2}$ cystine/mg protein)
- Able to swallow intact Cystagon capsule
- No clinically significant change from normal in liver functions tests (i.e., ALT and AST < 1.5 XULN and/or total bilirubin < 1.5 XULN) within past 6 months
- No clinically significant change in renal function (as measured by eGFR) within past 6 months
- Estimated GFR (correct for GSA) > 30 mL/min/1.73 m²
- Use of an acceptable form of contraception (sexually active female patients of childbearing potential only)

5.3.16 Exclusion Criteria

- Age < 6 years old or weight <21 kg
- Active inflammatory bowel disease or history of small bowel resection, cardiac disease (within 90 days of screening), active bleeding disorder (within 90 days of screening), history of malignant disease (within past 2 years)
- Hemoglobin < 10 g/dL at screening
- Patients on maintenance dialysis, renal transplant candidates, or post-renal transplant
- Allergy to hypersensitivity to cysteamine and penicillamine
- Pregnant (or planning to become pregnant) or lactating female patients

5.3.17 Endpoints

Primary Endpoint- WBC cystine level

The primary efficacy end point was a non-inferiority comparison of the depletion of steady-state cysteamine trough WBC cystine levels after treatment with Cystagon and RP103. The non-inferiority margin was pre-specified as < 0.3 for the upper limit of the 95.8% confidence interval between RP103 and Cystagon, corresponding to a p-value \leq 0.02104.

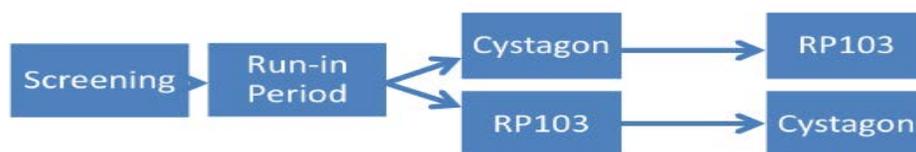
Other Endpoints

Secondary endpoints for the trial included quality of life (as measured by the PedsQL 4.0 scale) and swallowing (as measured by a visual analog score [VAS]). Use of concomitant gastric acid reduction therapies (e.g., antacids and/or PPIs) was an exploratory endpoint.

5.3.18 Treatment

This trial was comprised of a one-week screening period, 3-week run-in period and two 3-week treatment periods (see [Figure 5](#)).

Figure 5: RP103-03 Trial Schematic



During screening, a medical history was obtained to ensure that patients met eligibility criteria. Screening assessments included physical examinations, concomitant medications, height, weight, body mass index (BMI) and body surface area (BSA) calculations, vital signs, quality of life (PedsQL or SF-36), electrocardiogram (ECG),

laboratory assessments (chemistry, hematology, and urinalysis), VAS swallowing difficulty, an investigator-administered checklist of specific AEs, and pregnancy screening.

During the run-in period, patients continued receiving their stable dose of Cystagon. At the end of the run-in period, patients were randomized to their treatment sequence (Cystagon→ RP103 or RP103→ Cystagon). Randomization was stratified based on WBC cystine levels (≤ 1 nmol $\frac{1}{2}$ cystine/mg protein and >1 to <2 nmol $\frac{1}{2}$ cystine/mg protein). Screening assessments were repeated at the end of the run-in period (Day 21). In addition, adverse events and concomitant medications were assessed continuously during the run-in period. PK and PD sampling were performed during the second week of the run-in period (Days 3-5).

During the RP103 portion of the treatment period, patients received RP103 in an unblinded manner. Blinding was not feasible due to several factors including the inability of young children to swallow large over-encapsulated capsules, and the inability to mask the characteristic smell of cysteamine capsules or the halitosis that occurs shortly after cysteamine dosing. The total daily RP103 starting dose was initially 70% of the previous total daily Cystagon dose, with an allowed increase of up to 92% of the previous total daily Cystagon dose (25% increase). Patients enrolled into the trial after Amendment 4 received a total daily RP103 starting dose of 80% with an allowed increase of up to 100% of the previous total daily Cystagon dose.

During the treatment period, physical examinations, concomitant medications, weight, BMI and BSA calculations, vital signs, quality of life, ECG, laboratory assessments, VAS swallowing difficulty, AE checklist, AEs, and pregnancy screening were assessed during Weeks 4, 6, 7, and 9. PK and PD samples also were collected during Weeks 4, 6, 7 and 9 of the treatment period. Adverse events and concomitant medications were assessed continuously during the two treatment periods.

Patients were assessed during a follow-up visit one week after the end of treatment. All study assessments except for height, pregnancy screening, quality of life, and PK/PD sampling were performed during the follow-up visit.

Patients were also issued drug diaries in which to record daily study drug doses and dose times, as well as concomitant medications. Patients were to maintain the diaries beginning at screening through end the treatment period. Diaries were collected and reviewed at all clinic visits through the end-of-study visit.

[Table 11](#) details the schedule of assessments for RP103-03.

Table 11: RP103-03 Schedule of Assessments and Procedures

Evaluation	Screening	Run-In Period Cystagon							
		Week 1	Week 2						Week 3
Study Weeks	1-7	8-14						15-21 (+3)	
Study Days	1-7	8-14						15-21 (+3)	
Day	-7 to -1	1	2	3	4	5	6-7	1-6	7
Informed Consent/ Medical History	X								
Height	X								
Weight									X
BMI & BSA Calculations	X								X
Vital Signs	X			X	X	X			X
Physical Examination	X								X
Pregnancy Screening	X								X
Adverse Events	X	X	X	X	X	X	X	X	X
AE Checklist	X								X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Daily Drug Diaries	X	X	X	X	X	X	X	X	X
VAS Swallowing Difficulty	X								X
Quality of Life Questionnaire (PedsQL/SF-3)	X						X		X
ECG	X								X
Laboratory (chemistry, hematology, urinalysis)	X								X
Cystagon Administration	X	X	X	X	X	X	X	X	X
PK Sampling (cysteamine)				X	X	X			
PD Sampling (WBC cystine)				X	X	X			
Safety/PD Review									X

Source: RP103-03 Final Clinical Study Report (Amended) dated December 26, 2012

Table 11: RP103-03 Schedule of Assessments (cont'd)

Study Periods	Period 1 Cystagon or RP103														Period 2							Follow-up						
	Week 4						Week 5		Week 6						Week 7			Week 8				Week 9						
Study Days	22-28 (±3)						29-35 (±6)		36-42 (+6)						43-49 (+6)			50-56 (+9)				57-63 (+9)			64-70 (+11)			
Day	1	2	3	4	5	6-7	1-7	1-3	4	5	6	7	1	2	3	4	5	6	7	1-7	1-3	4	5	6	7	1-6	7	
Informed Consent/ Medical History																												
Height																												
Weight					X				X								X					X					X	
BMI & BSA Calculations					X				X								X					X					X	
Vital Signs					X				X								X					X					X	
Physical Examination					X				X								X					X					X	
Pregnancy Screening									X													X						
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE Checklist					X				X													X					X	
Daily Drug Diaries	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
VAS Swallowing Difficulty					X				X								X					X					X	
(PedsQL/SF-3)												X					X										X	
ECG					X				X								X					X					X	
Laboratory (chemistry, hematology, urinalysis)					X				X								X					X					X	
Cystagon or RP103 Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
PK Sampling (cysteamine)			X	X	X				X	X	X			X	X	X							X	X	X			
PD Sampling (WBC cystine)			X	X	X				X	X	X			X	X	X							X	X	X			
Safety/PD Review							X													X								

Source: RP103-03 Final Clinical Study Report (Amended) dated December 26, 2012

5.3.19 Concomitant Medications

There were no restrictions on the use of concomitant medications during the trial, with the exception of gastric acid reducing (GAR) medications. Patients who used GAR medications prior to the trial were permitted to continue these medications during the Cystagon treatment period. However, during the RP103 treatment period, patients were requested to limit their use of GAR medications to treatment of “intolerable” episodes of gastric upset.

5.3.20 Prohibited Medications

Illegal drug use and alcohol use were prohibited during the study. what about GAR?

5.3.21 Safety Considerations/Monitoring

Safety was assessed by AEs and AE Checklist inquiries, clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, concomitant medications, vital signs, and ECGs.

Safety results were reviewed by the trial investigator. There was no independent Data Monitoring Committee chartered for the study. Safety-related criteria for withdrawal of an individual patient included: change in eligibility status, AEs, adverse laboratory events, intercurrent illness, and lack of compliance with study visits or protocol requirements. Criteria for termination of the study or an individual study site included the discovery of an unexpected, significant or unacceptable risk to the patients.

5.3.22 Statistical Analysis Plan

The Statistical Reviewer, Behrang Vali, did not identify any significant issues with the analytical assumptions or models used in the trial.

Analysis Populations

Three trial populations were defined for data analysis:

- Intent-to-Treat (ITT): all randomized patients
- Per Protocol (PP): all patients in the full efficacy analysis except patients who had average WBC cystine levels > 2 nmol ½ cystine/mg protein while being treated with Cystagon during the run-in or treatment periods
- Safety population: all patients who received at least one dose of study drug (RP103 or Cystagon)

Table 12: RP103-03 Data Sets Analyzed

Patients Randomized	43 (100 %)
Patients in Efficacy Analysis Population	41 (95%0
Patients in Safety Population	43 (100 %)
Patients in Per Protocol Population	39 (91 %)
Patients in PK/PD Analysis Population	39 (91%)

Source: A RP103-03 Final Clinical Study Report (Amended) dated December 26, 2012

The applicant performed all efficacy analyses using the PP population. For the primary efficacy analysis, 39/43 patients (88%) who enrolled in the trial were included in the PP population. Four patients were excluded from the PP population, including two siblings who discontinued from the study (Patients 01002 and 01003; see [Section 5.3.23](#) [Patient Disposition] for further details) and two patients (Patients 02014 and 03009) who did not meet the WBC cystine level criteria for the PP population.

Comment: The Applicant's definitions of the analysis populations are consistent with the definitions for analysis sets contained in ICH E9 "Statistical Principles for Clinical Trials."

Determination of Sample Size

The trial SAP called for a re-estimation of sample size based on intra-subject variance of WBC cystine levels once 20 evaluable patients completed the study to achieve a minimum enrollment of 30 patients and a maximum enrollment of 50 patients. The initial sample size re-estimation indicated that 30 patients were needed. A second sample size re-estimation was performed due to the discovery of a calculation error in the reporting of WBC cystine levels. The second re-estimation indicated that a total sample size of 36 patients was required to achieve 90% power for a test at the 0.04208 significance level (two-sided α).

The primary efficacy endpoint was a non-inferiority comparison of the reduction of WBC cystine levels (measured at drug trough levels under steady-state conditions) after treatment with Cystagon and RP103. The primary efficacy analysis was performed using repeated measures ANOVA (i.e., linear mixed effect model) with no imputation of missing data.

Additional analyses

Secondary efficacy endpoints were analyzed with no multiplicity adjustment. The applicant presented summary statistics for baseline/demographic, efficacy, and safety data.

Analysis of Primary Endpoint

The use of WBC cystine as the primary efficacy endpoint for the trial is acceptable. The guidance *Applications Covered by Section 505(b)2* states that a 505(b)2 application may include "appropriate bridging studies" if these studies "provide an adequate basis

for reliance upon FDA's finding of safety and effectiveness of the listed drug(s)."⁸ IN this reviewer's opinion, demonstration of a comparable effect on this pharmacodynamic marker meets the 505(b)2 application requirements for information to demonstrate efficacy.

Of note, WBC cystine would not be acceptable as the primary efficacy endpoint for a "stand-alone" approval since a relation between WBC cystine levels and clinical outcomes has not been established. The efficacy of the reference product was established using clinical endpoints (renal function and growth). Survival analyses for these trials indicated that early initiation of treatment appeared to be the most important factor in preventing renal disease progression. WBC cystine response was also evaluated. Although WBC cystine levels were reduced with treatment, survival analyses of patients followed-up for up to 10 years indicated that prevention of end-stage renal disease was not dependent on cysteamine dose levels or failure to reduce WBC cystine levels to <2 nmol ½ cystine/mg protein. Similarly, a recently published observational 20-year study of 23 patients (a majority of whom were pediatric patients) reported a lack of correlation between WBC cystine levels and renal disease progression, although there appeared to be a correlation between cysteamine dose and renal disease progress. The authors attributed their failure to find a WBC cystine level correlation to their analysis being underpowered due to missing data for some patients.⁹

Other data suggest that there is a correlation. Gahl et al conducted a retrospective analysis of non-renal complications in 100 adult patients with nephropathic cystinosis. Fewer complications were observed in patients who received "adequate" cystine depletion therapy (defined by WBC cystine levels or by length of therapy for patients for whom WBC cystine data were not available).¹⁰

Thus, data on the correlation of WBC cystine levels and clinical outcomes are not consistent. The reasons for the differences between the aforementioned studies are not clear. Differences in study design, study populations (pediatric versus adult patients); and clinical endpoints (renal versus non-renal) may account for some of the differences in findings. Another potential factor may be that WBC cystine data were obtained from multiple sites that used differing methodologies and reference standards.

The clinical rationale for the non-inferiority margin set for the trial was not well-articulated. In the clinical study report for RP103-01, the applicant notes that the study design for RP103-03 was informed by a University of San Diego (UCSD) study of seven

⁸ See the guidance for industry *Applications Covered by Section 505(b)2* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>)

⁹ Greco M, Brugnara M et al, Long-term outcome of nephropathic cystinosis: a 20-year single-center experience, *Pediatr Nephrol* 2010; 25: 2459-2467.

¹⁰ Gahl W, Balog JZ et al, Nephropathic cystinosis in adults natural history and effects of oral cysteamine therapy, *Ann Intern Med* 2007; 147: 242-250.

pediatric patients with nephropathic cystinosis treated with a cysteamine 12-hour delayed-release formulation as the ¹¹ In the UCSD study, WBC cystine levels were evaluated in patients who were on a stable dose of Cystagon at study entry. The PK/PD profile of the delayed-release product was evaluated after a single dose and at steady state. The mean WBC cystine level at baseline was $0.7 + 0.3 \text{ nmol } \frac{1}{2}$ cystine/mg protein. At steady-state, a mean daily dose of the delayed-release product equal to 60% of the mean daily dose of Cystagon resulted in a mean WBC cystine level of $0.41 \pm 0.22 \text{ nmol } \frac{1}{2}$ cystine/mg protein.

Reviewer's Comments:

From the above data, it appears that the non-inferiority margin was based primarily on the results of this single small study and represents a non-inferiority margin that approaches the entire assumed effect of Cystagon.¹² However, because of the potential for improved compliance with cystine depletion therapy using a delayed-release product, this reviewer considers a large non-inferiority margin to be clinically acceptable if the safety profile of RP103 is similar to or more favorable than the safety profile of Cystagon.

Overall, the trial design for RP103 meets the regulatory requirements for adequate and well-controlled trials as delineated in 21 CFR 314.126. The study objectives are clearly defined. The trial design (randomized, crossover trial) is acceptable, since use of a placebo control would be unethical in this patient population and the primary endpoint for the trial is an objective measurement. The trial design includes appropriate measures to minimize bias, including eligibility criteria that reduced heterogeneity in the study population, randomization, and a prospective statistical analysis. As discussed earlier, a blinded study design was not feasible due to formulation issues (inability of children to swallow over-encapsulated capsules) and the inability to mask the sulfurous smell of drug metabolites that are excreted via the lungs.¹³

Currently there are very limited data for review in pediatric patients under 6 years old. Therefore, results from this study cannot be used to evaluate treatment effect differences in infants and young children. The applicant has proposed a pediatric study to evaluate the efficacy and safety of RP103 in this population, but this study has not yet been initiated.

¹¹ Dohil R, Fidler M et al, Twice-daily cysteamine bitartrate therapy for children with cystinosis, *J Pediatr* 2010; 156: 71-75.

¹² The guidance for industry *Non-Inferiority Clinical Trials* notes that it is generally desirable to choose a smaller value (M_2) for the non-inferiority margin than the entire assumed effect of the action control in the non-inferiority trial (M_1).

¹³ Besouw M, Blom H et al, The origin of halitosis in cystinotic patients due to cysteamine treatment, *Mol Genet Metabol* 2007; 91: 228-233.

5.3.23 Patient Disposition

Patient Disposition

Forty-four (44) of 45 patients screened (including seven patients who were screened twice) were eligible and enrolled into the trial. There was one screening failure due to the patient having an elevated WBC cystine level during the run-in period.

Discontinuations

Of the 44 patients enrolled into the trial, 43 patients were randomized to one of the two treatment sequences; one patient was discontinued prior to randomization (physician's decision). Two patients who were siblings were discontinued during the course of the study. One sibling (Patient 01002) was discontinued due to a non-treatment related AE (cellulitis post-operatively after planned surgery); her family elected to simultaneously discontinue the other sibling (Patient 01003) because they no longer wanted to travel the long distance to the study site. Forty-one patients completed the study. [Table 13](#) summarizes the patient populations for the study.

Table 13: RP103-03 Patient Disposition

Disposition	Total
Patients Randomized	43 (100 %)
Patients Who Completed Study	41 (100 %)
Patients Who Discontinued from Study	2 (5 %)
AE	1 (2%)
Other (travel issues)	1 (2%)
Patients Who Enrolled in RP103-04 (extension trial)	40 (93%)

Source: RP103-03 Final Clinical Study Report (Amended) dated December 26, 2012

5.3.24 Protocol Violations and Deviations

Seven major protocol deviations were reported for seven patients including four patients with deviations from eligibility criteria (4 patients), deviations or non-compliance in study drug dosing (2 patients), and deviation in randomization (one patient). [Table 14](#) lists the major protocol deviations.

Table 14: RP103-03 Major Protocol Deviations

Patient ID #	Visit	Deviation Category	Deviation Description
02014	Period 1 Week 4	Non-compliance	Patient not taking study drug
02104	Screening Week 1	Eligibility	WBC cystine level >2
02109	Screening Week 1	Eligibility	Patient weight < minimum weight of 21 kg
03101	Period 1 Week 5	Procedure Not Done	Patient randomized prior to review of PD results
06003	Period 1 Week 4	Study Drug Dosing	Drug dosing was suspended for 3 days due to SAE
07005	Screening Week 1	Eligibility	Patient weight < minimum weight of 21 kg
08001	Screening Week 1	Eligibility	Alkaline phosphatase level > allowed value

PD=pharmacodynamics; SAE=serious adverse events

Source: RP103-03 Final Clinical Study Report (Amended) dated December 26, 2012

Minor protocol deviations included missed assessments or assessment performed outside the protocol window (39 patients), missed study drug doses (8 patients), and errors in study dose administration including not taking the drug after a meal (7 patients), taking the incorrect dose and/or taking the drug at the incorrect time (6 patients).

5.3.25 Patient Compliance

Eight patients were reported to have missed study doses during the trial, based on patient self-report or medication counts performed during clinic visits. Three patients (02104, 06003, and 07002) missed one or more consecutive days of study dosing (i.e., ≥ 4 consecutive doses of Cystagon or ≥ 2 consecutive doses of RP103). The remaining five patients missed less than one day of study dosing. [Table 15](#) summarizes information on patient missing study drug doses.

Table 15: RP103-03 Patients Missing Doses of Study Drug

Patient ID	Drug	# doses missed	Visit	Comment
01005	Cystagon	1 1	Period 2 Week 7 Day 3 Period 2 Week 7 Day 4	Patient vomiting, refused doses
02003	Cystagon	4	Period 1 Week 6 Day 4	Patient missed 4 doses over 2 days
02014	Cystagon	NS	Period 1 Week 4 Day 3	Patient not taking medicine. Only witnessed doses taken by patient were final 3 days of study (Period 2, Week 9, Days 5-7)
02109	Cystagon	1	Follow-up Day 7	Patient missed 1 dose
06003	RP103	NS	Period 1 Week 4 Day 3	Drug not taken for 3 days due to SAE
07002	RP1003	NS	Period 3 Week 9 Day 4	Missed study drug doses during hospitalization for surgical repair of leg fracture
09001	RP1003	NS	Period 1 Week 4 Day 3	Returned 3 extra capsules for medication count
09004	Cystagon Cystagon	NS	Run-in Period Week 2 Day 3 Period 2 Week 7 Day 3	Returned 1 extra capsule for medication count Returned 1 extra capsule for medication count

Source: RP103-03 Final Clinical Study Report (Amended) dated December 26, 2012, Appendix 16.2.2.4 and eCFR for patient 07002

5.3.26 Review of RP103-03 Study Results

A. Demographics

The mean age of patients in the trial was 12 years (range 6 years to 26 years). The mean body surface area (BSA) and daily Cystagon dose for patients in the PP population were 1.18 m² and 1.8 g/m²/day, respectively. Four of 43 (9%) patients in the intent to treat (ITT) population (n=43) were excluded from the PP population (n=39). The demographic characteristics of the per protocol (PP) population were similar to those of the ITT population in terms of age (mean/median age was 11.7/11.0 years for the ITT population), proportion of patients by gender, and proportion of patients by age cohorts. [Table 16](#) summarizes patient baseline data.

Table 16: RP103-03 Demographics and Baseline Disease Characteristics (per Protocol Population)

Characteristic	Overall n=39
Age (years) N Mean \pm SD Median Min,Max	39 11.9 \pm 4.3 11.0 6,26
Age Cohorts (years) 6-12 13-17 \geq 18	23 (59%) 13 (33%) 3 (8%)
Gender [n(%)] Male Female	23 (59%) 16 (41%)
Race [n(%)] Caucasian Other	38 (97%) 1 (3%)
Weight (kg) N (%) Mean \pm SD Median Min,Max	39 36.4 \pm 14.8 32.6 19.3, 88.5
BSA (m²) N (%) Mean \pm SD Median Min,Max	39 1.18 \pm 0.31 1.13 0.77, 2.06
Run-in Period WBC Cystine Levels (nmol $\frac{1}{2}$ cystine/mg protein) N LS Means \pm SE Median Min,Max	39 0.49 \pm 0.26 0.49 0.09, 1.22
Run-in Period WBC Cystine Level Ranges [n(%)] N \leq 1 nmol $\frac{1}{2}$ cystine/mg protein LS Means \pm SE Median Min,Max >1 to <2 nmol $\frac{1}{2}$ cystine/mg protein LS Mean \pm SE Median Min,Max	39 37 (95%) 0.39 \pm 0.39 2 (5%) 1.24 \pm 0.11
Run-in Period Total Daily Cystine Dose (g/m²/day) N Mean \pm SD Median Min,Max	39 1.60 \pm 0.34 1.59 0.8, 2.34

LS=Least Squares

Source: Applicant's submission

B. Concomitant Medications

Concomitant medications were recorded using standardized WHO Anatomical Therapeutic Chemical (ATC) classification codes. All randomized patients (n=43) received at least one concomitant medication. The most common (>20% overall) therapeutic classes of concomitant medications in the trial were amino acid derivatives (93%), potassium (86%), Vitamin D/Vitamin D analog (58%), antacids with sodium bicarbonate (35%), ACE inhibitors (33%), somatropin/somatropin agonists (28%) and calcium in combination with other drugs (23%). Most patients continued on the same concomitant medications throughout the study.

C. Review of Efficacy

Efficacy Summary

The trial results established non-inferiority of RP103 compared to Cystagon. The results of the statistical analysis of the primary endpoint in the per protocol population were least squares means (\pm SE) values for RP103 and Cystagon of 0.52 and 0.44 nmol $\frac{1}{2}$ cystine/mg protein, respectively, with a difference of 0.08 ± 0.03 nmol $\frac{1}{2}$ cystine/mg (p -value <0.001). Using the same analysis in the ITT population, least squares means (\pm SE) values for RP103 and Cystagon were 0.53 and 0.74 nmol $\frac{1}{2}$ cystine/mg protein, respectively, with a difference of -0.21 ± 0.13 nmol $\frac{1}{2}$ cystine/mg protein. Thus, both analyses demonstrated a difference in WBC cystine values for RP103 within the non-inferiority margin of 0.3 nmol $\frac{1}{2}$ cystine /mg protein.

There were no consistent patterns of treatment effect noted for difficulty swallowing or quality of life. Interpretation of the study data was limited due to lack of information on the patient's clinical status prior to treatment with Cystagon and duration of treatment with Cystagon prior to trial entry. In addition, the trial duration was likely too short to assess for changes in these endpoints.

There were fewer reported episodes of treatment with gastric acid-reducing (GAR) medications (predominantly PPIs) and fewer patients who reported taking GAR medications during the RP103 treatment period compared with the Cystagon treatment period. However, statistical analysis was not performed for this endpoint since patients were not randomized into the study by GAR medication use. In addition, GAR medications use during the RP103 treatment period was restricted to treatment of "intolerable" symptoms. Therefore, it is not possible to directly compare GAR medications use between the two drug products.

1. Primary Efficacy Endpoint.

The results of the primary efficacy analysis (non-inferiority comparison of RP103 to Cystagon in terms of WBC cystine levels) are summarized in [Table 17](#). The mean WBC cystine level was less than 1 nmol $\frac{1}{2}$ cystine/mg protein during both treatment periods;

with values of 0.4367 nmol ½ cystine/mg protein and 0.5152 nmol ½ cystine/mg protein for the Cystagon and RP103 treatment periods, respectively. The mean difference was 0.0785 nmol ½ cystine/mg protein, with a 95.8% CI of 0.0107 to 0.1464, which was within the non-inferiority margin of 0.3 nmol ½ cystine /mg protein.

Table 17: Statistical Analysis of Pharmacodynamic Parameters of WBC Cystine (nmol ½ cystine/mg protein) (Per Protocol and ITT Populations)

Treatment	N	LS Means (SE)	Difference of LS Means* (SE)	SE of LS Mean Difference	T-Value for CI (DF=37)	95.8% CI of LS Means Difference	P-Value
Per Protocol Population							
Cystagon	39	0.4367 (0.05555)	0.0785	0.0323	2.1037	0.0107 to 0.1464	<0.0001
RP103	39	0.5152 (0.05555)					
ITT Population							
Cystagon	41	0.7355 (0.13838)	-0.2089	0.1285	2.1000	-0.4788 to 0.0609	
RP103	43	0.5266 (0.13740)					

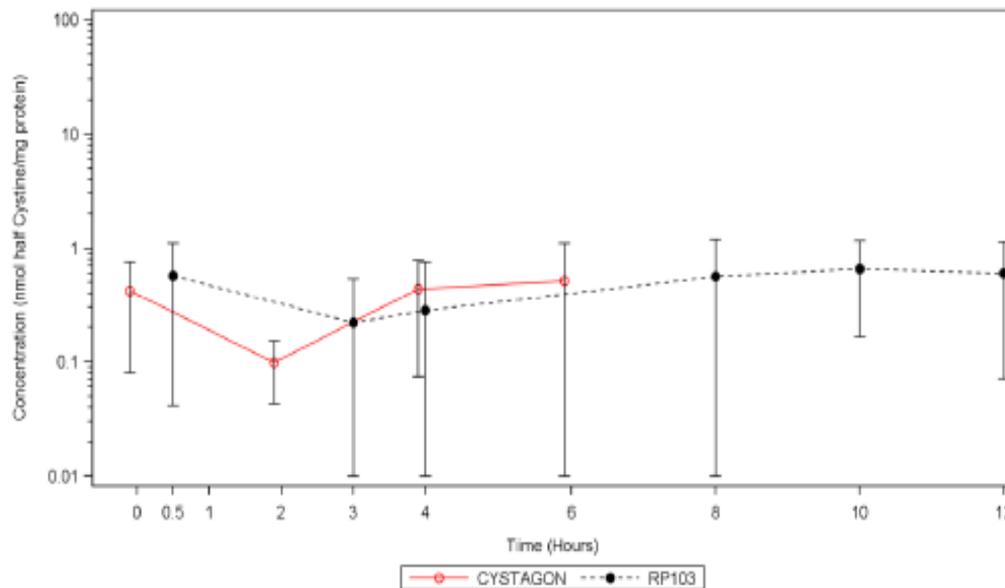
S=least squares; SE=standard error; DF= degrees of freedom; CI= confidence interval

*Difference= RP103 LS means minus Cystagon LS means

Source: Applicant's RP103-03- FDA Request Tables and Figures dated January 30, 2013

The applicant also provided a semi-logarithmic plot of WBC cystine concentrations versus time (see [Figure 6](#)) that demonstrated that WBC cystine levels were maintained below 1 nmol ½ cystine/mg protein during the study drug dosing intervals (i.e., 6 hours for Cystagon and 23 hours for RP103).

Figure 6: Mean (+SD) Concentrations of WBC Cystine (nmol ½ cystine/mg protein) vs. Time (Per Protocol Population; Semi-Log Scale)



Source : RP103-03 Final Clinical Study Report (Amended) dated December 26, 2012, Figure 14.2.1.3)

2. Secondary Endpoints

Quality of Life

Quality of life was measured using the SF-36 scale in adult patients (n=3) and the PedsQL 4.0 Generic Core Scale in pediatric patients (n=36). The PedsQL 4.0 is a quality of life scale that measures four functional areas (physical, emotional, social, and school functioning). The scale is available in age-appropriate instruments with child self-report and parent proxy-report formats. This instrument has been used to evaluate quality of life in healthy children and in children with chronic health conditions. The mean PedsQL 4.0 score in large cohort studies of healthy children (n=5480) was 84 (out of a possible score of 100), while lower scores were reported in children with chronic conditions.¹⁴

The applicant reported pediatric data by three age cohorts: ages 5 to 7 years, ages 8 to 12 years, and ages 13 to 18 years.¹⁵ Mean baseline scores in all pediatric age cohorts were lower than mean scores in healthy children reported in the literature. However, there was wide inter-patient variability in scores in each age cohort. Some patients reported scores indicating poor functioning while other patients reported scores indicating

14 Varni JW et al, Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales, *Health and Quality of Life Outcomes* 2007; 5:43

15 The PedsQL 4.0 has child self-report instruments for ages 5-7, 8-12, and 13-18 years and parent proxy-report instruments for ages 2-4, 5-7, 8-12, and 13-18.

normal functioning. The applicant noted that interpretation of the data was limited, due to the small number of pediatric patients (10 patients or less) each of the three age cohorts during the two treatment periods. [Table 18](#) summarizes PedsQL 4.0 scores.

Table 18: RP103-03: Quality of Life (PedsQL 4.0 Generic Core Scale) Scores During Run-in Period and Treatment Periods

Age Cohort	PedsQL 4.0 Scores (0-100 scale)				
	End of Run-in Period	End of Period 1		End of Period 2	
		Cystagon	RP103	Cystagon	RP103
5-7 Years					
N	N=8	N=3	N=4	N=5	N=2
Mean (\pm SD)	75 \pm 24	74 \pm 36	77 \pm 20	78 \pm 17	62 \pm 51
Median	75	91	75	70	62
Min,Max	(28,100)	33, 98	56, 100	63, 100	26, 98)
8-12 years					
N	N=13	N=5	N=9	N=5	N=6
Mean (\pm SD)	79 \pm 13	73 \pm 14	85 \pm 11	86 \pm 9	74 \pm 14
Median	82	65	86	86	71
Min,Max	(50, 96)	59, 90)	86 61, 99)	75, 99)	61, 97)
13-18 years					
N	N=14	N=11	N=3	N=4	N=10
Mean (\pm SD)	75 \pm 13	76 \pm 12	84 \pm 18	86 \pm 12	78 \pm 14
Median	76	76	93	86	81
Min,Max	51, 91	54, 95	64, 96)	72, 100)	59, 95)

Reviewer Comments:

There do not appear to be any consistent patterns in change from baseline in quality of life in either treatment group. Scores were similar in the youngest age cohort throughout the course of the trial in both treatment groups. There were conflicting results for QoL scores in the older age cohorts. In period 1, older children and adolescents in the RP103 treatment group reported improved scores. Conversely, in period 2, older children and adolescents in the Cystagon treatment group reported improved scores. This reviewer agrees with the applicant that the small sample size in each age cohort limits interpretation of the data. In addition, no data were available on the clinical status of these patients prior to initiation of Cystagon treatment or the duration of Cystagon treatment prior to study entry. Finally, the 9-week trial period may not have been long enough to assess for a difference in treatment effect on functioning between Cystagon and RP103, particularly since the majority of patients in the trial had normal baseline functioning (i.e., score 84 or higher [mean PedsQL 4.0 score in healthy children reported in the literature]).

VAS Difficulty Swallowing

Swallowing difficulties were measured using a 10-point visual analog scale, with 2-point increments in scoring from 0 [no pain] to 10 [very much pain]). Visual analog scales have been established as a reliable and valid method for assessing pain in children as young as 5 years of age.¹⁶

A majority of patients reported no difficulty or minimal difficulty swallowing throughout the course of the study. Eight of 39 patients (21%) reported a VAS score of ≥ 4 at one time point during the study; only 3/39 patients (8%) reported VAS scores of ≥ 4 at more than one time point during the study. There were no clear differences in the reported degree of difficulty swallowing between the two treatment groups. The applicant stated that the VAS findings suggested that prior treatment with Cystagon had achieved good control of swallowing difficulty and that this control was sustained during the crossover treatment period. [Table 19](#) summarizes VAS Difficulty Swallowing scores.

Table 19: RP103-03: VAS Difficulty Swallowing Scores During Run-in Period and Treatment Periods

VAS Difficulty Swallowing Score (0-10 scale)*	Run-in end	Period 1		Period 2	
	All patients N=39	Cystagon N=21	RP103 N=19	Cystagon N=21	RP103 N=20
VAS Score= 0	30	11	13	11	12
VAS Score= 2	8	9	5	5	6
VAS Score= 4	1	1	1	4	1
VAS Score= 6	0	0	0	1	0
VAS Score= 8	0	0	0	0	1
VAS Score= 10	0	0	0	1	0

*Score represents highest VAS score reported during the report period for each patient

Reviewer Comments:

As discussed earlier, these findings are difficult to interpret due to lack of information on patient clinical status prior to initiation of Cystagon treatment and the duration of Cystagon treatment prior to study entry. Thus, it is not possible to determine whether the low VAS scores observed in most patients at baseline represented a treatment effect with Cystagon or were due to mild underlying disease. In addition, it is unclear whether any changes in swallowing function would be expected to occur during the 9-week time frame of the trial.

16 McGrath PA, Seifer CE et al., A new analogue scale for assessing children's pain: an initial validation study, *Pain* 1996; 64:435-443.

Use of Gastric Acid-Reducing (GAR) Medications

The applicant noted that fewer patients appeared to use GAR medications (primarily proton pump inhibitors) during the RP103 treatment period (5/39 patients) compared to the Cystagon treatment periods (19/39 patients) and that there were fewer episodes of GAR medication use with RP103 (70 episodes) compared with Cystagon (477 episodes). However, no statistical analysis was performed since patients were not randomized into the study by GAR medication use.

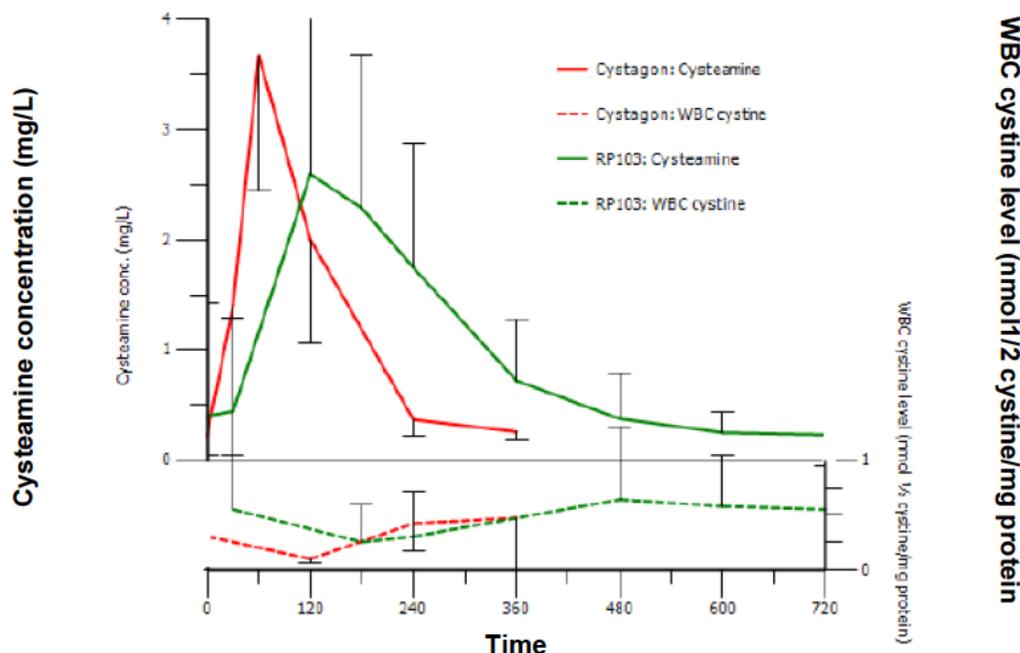
Reviewer Comments:

There was an almost 7-fold difference in the use of GAR medications between the Cystagon treatment period and the RP103 treatment period, suggesting that RP103 had a treatment sparing effect in terms of concomitant GAR medications usage. However, as noted by the applicant, use of GAR medications was not included in the randomization scheme for the study. In addition, the conditions of GAR administration were different for the RP103 period compared to conditions of administration during screening or during the Cystagon treatment period. During the RP103 treatment period, GAR use was restricted to treatment of “intolerable” symptoms. Therefore, it is not possible to directly compare GAR use between the two drug products.

3. Drug Dose Response Relationship

The applicant performed PK/PD analyses using a population PK model combined to an inhibitory E_{\max} model for PD (see [Figure 7](#)). The PK/PD analysis set included 39/43 (91%) of randomized patients.

Figure 7: RP103-03: PK/PD Model of Average Cysteamine Concentration & Average WBC Cystine Level after a Single, Variable Dose of Cystagon or RP103 at Steady State*



*PK/PD Model: 2-compartment population PK model; inhibitory Emax PD model

Source: Applicant's Population PK/PD Modeling Report, Figure 8

The PK/PD model demonstrates a correlation between cysteamine concentration and WBC cystine response. However, the Pharmacometrics reviewer noted that the model had limited utility for determining dosing recommendations since the model did not evaluate covariate effects (age, gender, etc.) or the dose increase required to achieve a meaningful reduction in WBC cystine. As discussed in [Section 4.4.3](#), dose-response analyses evaluating time-averaged doses of Cystagon and RP103 indicated that WBC cystine response was reduced with RP103 doses that were lower than the prior Cystagon dose.

4. Subpopulations

The applicant performed an analysis of the primary endpoint by gender (see [Table 20](#)). RP103 appeared to produce a greater WBC cystine response compared to Cystagon in females. No age group analysis was performed due to the small number of adults enrolled in the study (n=3).

Table 20: Statistical Analysis of Pharmacodynamic Parameters of WBC Cystine (nmol ½ cystine/mg protein) by Gender (Adjusted for Stratification)

Treatment	N	LS Means (SE)	Difference of LS Means	SE of LS Mean Difference	T-Value for CI (DF=37)	95.8% CI of LS Means Difference
Males						
Cystagon	23	0.4536 (0.05555)	0.05938	0.1227	0.0375	0.0417 to 0.2036
RP103	24	0.5762 (0.05924)				
Females						
Cystagon	18	1.1837 (0.30153)	-0.6923	0.2900	2.1981	-1.3298 to -0.0548
RP103	19	0.4914 (0.29668)				

S=least squares; SE=standard error; DF= degrees of freedom; CI= confidence interval

*Difference= RP103-Cystagon

Source: Applicant's RP103-03- FDA Request Tables and Figures dated January 30, 201

RP103-04 (Extension study)

5.3.27 General Design and Objectives

This is a 24-month, open-label, multicenter trial to evaluate the long-term safety, tolerability, PK and PD of RP103 in nephropathic cystinosis patients.

The primary objective of the trial was to assess long-term safety and tolerability of RP103 in nephropathic cystinosis patients. The secondary objectives of the trial were to assess the steady-state PKD and PD of RP103 and to assess long-term quality of life. This trial was conducted in nine sites in three countries: France, Netherlands, and United States. The trial began in August 2010 and is ongoing.

There were five amendments of the protocol during the course of the trial. As discussed in Section 3.1, major amendments included:

- modification of eligibility criteria to allow enrollment of other patients in addition to patients who had completed RP1203-03,
- establishment of study drug starting dose (70% of stable Cystagon dose) and allowed dose adjustments (allowed increase of up to 100% of Cystagon dose) for non-RP103-03 patients
- modification of drug administration conditions,
- changes in WBC cystine level measurement and reporting of result

- changes in study assessments (elimination of GSRS, change to investigator-administered pediatric QoL instrument)

5.3.28 Inclusion Criteria

- Male and female nephropathic cystinosis patients who completed RP103-03 or male and female patients with a documented diagnosis of cystinosis
- Able to swallow intact Cystagon capsule
- No clinically significant change from normal in liver functions tests (i.e., ALT and AST < 1.5 XULN and/or total bilirubin < 1.5 XULN) within past 6 months
- No clinically significant change in renal function (as measured by eGFR) within past 6 months
- Estimated GFR (correct for GSA) > 30 mL/min/1.73 m²
- Use of an acceptable form of contraception (sexually active female patients of childbearing potential only)

5.3.29 Exclusion Criteria

- Failure to complete RP103-03 (RP103-03 patients only)
- Active inflammatory bowel disease or history of small bowel resection, cardiac disease (within 90 days of screening), active bleeding disorder (within 90 days of screening), history of malignant disease (within past 2 years)
- Hemoglobin <10 g/dL at screening
- Allergy to hypersensitivity to cysteamine and penicillamine
- Pregnant (or planning to become pregnant) or lactating female patients
- Patients unable or unwilling to comply with the protocol

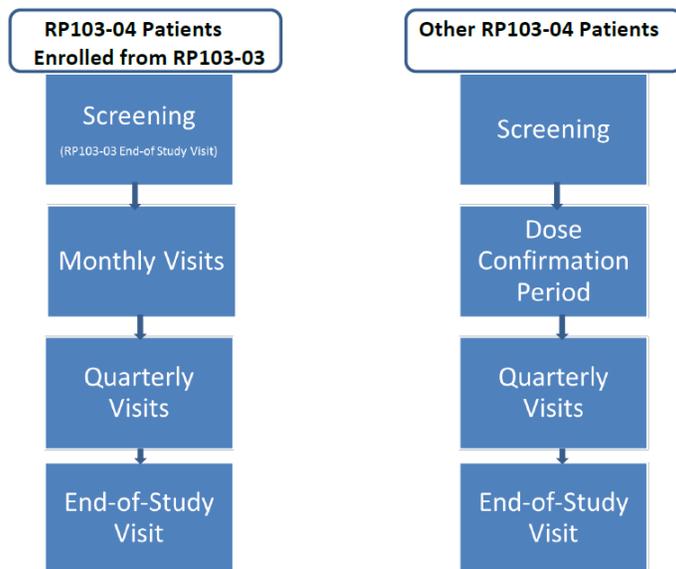
5.3.30 Endpoints

As noted earlier, the primary endpoint for the study was safety. WBC cystine levels over time (up to 24 months) were evaluated as a secondary endpoint. Exploratory endpoints included quality of life (as measured by PedsQL 4.0 or SF-36 scores) and swallowing difficulty (as measured by VAS scores).

5.3.31 Treatment

The trial has two schedules of trial assessments, based on whether or not patients enrolled into the trial after completing RP103-03 (see [Figure 8](#)).

Figure 8: RP103-04 Study Trial Schematic



Both sub-groups of patients undergo assessments during a screening visit, quarterly visits, and an end-of study visit. For patients who enrolled from RP103-03, the end-of study visit for RP103-03 served as the screening visit for RP103-04. Following screening, patients enrolled from RP103-03 were required to complete a minimum of six monthly study visits during a period in which all patients were being transitioned to a fixed quarterly visit schedule (visits must be scheduled by mid-month each January, April, July, and October). Some RP103-03 patients completed up to nine monthly visits. Patients were continued on the same RP103 dose that they received at the end of RP103-03.

Following screening, patients who had not completed RP103-03 must complete a 5-day dose confirmation period and then these patients are entered directly into the quarterly visit schedule.

[Table 21](#) summarizes the schedule of assessments for RP103-04.

Table 21: RP103-04 Schedule of Assessments and Procedures

Procedure	Study Visits					
	Screening	Dose Confirmation Period		Visit Frequency		End of Study (7±2 Days)
	Day -28 to Day -1	Day 1	Day 4 & 5	Monthly (+7 Days)	Quarterly (+ 7 Days)	
Number of Study Visits From RP103-03/New Patients	1/1	1/1	0/2	6 to 9/0	5 to 6/8	1
Inclusion/Exclusion Criteria	X	X				
Demographics	X					
Medical History/Medication History	X	X				
Serum Pregnancy Testing	X	X		X	X	
Height/Weight	X	X		X	X	X
BMI/BSA Calculation	X	X		X	X	X
Physical Examination	X	X		X	X	X
Clinical Laboratory Test	X	X		X	X	X
ECG	X	X		X	X	X
Vital Signs	X	X	X	X	X	X
PedsQL/SF-36	X	X		X	X	X
VAS Swallowing Difficulty	X	X		X	X	X
Daily Diary Medications Log	X	X		X	X	
Daily Diary Collection		X		X	X	X
Food/Liquid Intake Control		X	X	X	X	X
PK/PD Sample Collection	X	X	X (post-dose)	X	X	X
Investigator Review of Safety & PK/PD Data			X	X	X	
Concomitant Medications	X	X	X	X	X	X
AE Monitoring	X	X	X	X	X	X

Source: RP103-04 Interim Clinical Study Report (Amended) dated January 10, 2013

5.3.32 Concomitant Medications

Patients who were on Cystagon prior to trial entry were requested to stop taking gastric acid reduction medications at least 12 hours before receiving RP103 and to refrain from their use until completion of treatment with RP103. However, patients were allowed to take these medications in cases of intolerable gastric upset, at the investigator's discretion. There were no restrictions on the use of other concomitant medications during the trial.

5.3.33 Prohibited Medications

Illegal drug use and alcohol use were prohibited during the study

5.3.34 Safety Considerations/Monitoring

Safety was assessed by adverse events (AEs) and serious adverse events (SAEs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, vital signs, and ECGs.

5.3.35 Statistical Analysis Plan

The Statistical Reviewer, Behrang Vali, did not identify any significant issues with the analytical assumptions or models used in the trial.

Analysis Populations

Two trial populations were defined for data analysis:

- Safety population: all patients who received at least one dose of study drug (RP103)
- PK/PD population: all patients who had at least one PK/PD measure

Table 22: RP103-04 Data Sets Analyzed

Patients Randomized	48 (100 %)
Patients in Safety Population	48 (100 %)
Patients in PK/PD Analysis Population	48 (100%)

5.3.36 Patient Disposition

Patient Disposition

Forty of 41 patients (98%) who completed RP103-03 enrolled into RP103-04. Eight new patients, including seven pediatric patients and one adult renal transplant patient were enrolled into RP103-04 at the time of this submission. No patients had completed the trial at the time of this submission.

Discontinuations

Two patients (both were prior RP103-03 patients) were discontinued during the course of the study due to AEs (vomiting; decreased appetite and dyspepsia).

Table 23: RP103-04 Patient Disposition

Disposition	Total N=48)
Patients Randomized	
RP103-03 patients	40 (83 %)
Other patients	8 (17 %)
Patients Who Completed Study	0
Patients Who Discontinued from Study	2 (5 %)
AE	2 (4 %)

Source: RP103-04 Interim Clinical Study Report (Amended) dated January 10, 2013

5.3.37 Protocol Violations and Deviations

Eight major protocol deviations were reported for six patients, including interruptions or non-compliance in study drug dosing (4 patients), deviations in enrollment or screening procedures (2 patients), and errors in study drug administration (1 patient). There were no major protocol deviations from eligibility criteria. [Table 24](#) lists the major protocol deviations.

Table 24: RP103-04 Major Protocol Deviations

Patient ID #	Visit	Deviation Category	Deviation Description
01001	Quarterly 1 Week 4	Other	Patient & parents signed assent/consent forms not approved by IRB; proper assent/consent obtained at later visit
01004	Monthly 3	Non-Compliance	Parents suspended RP103 dosing due to worsening vomiting; Cystagon administered 3 days instead.
	Monthly 4	Non-Compliance	Parents suspended RP103 dosing due to worsening vomiting; Cystagon administered 1 week instead.
01301	Monthly 2	Study Drug Administration	Patient took non-intact RP103 capsule with juice for morning dose intermittently between during month.
06003	Monthly 1	Study Drug Dosing	Cystagon administered ~ 2weeks due to RP103 re-supply issue.
07002	Screening	Procedure Not Done	PK sample 15 minutes before RP103 dosing not collected.
08001	Monthly 1	Study Drug Dosing	Cystagon administered 5 days due to unavailability of RP103; dosing times/dates not recorded in patient diary.
	Monthly 2	Study Drug Dosing	Cystagon administered 18 days due to unavailability of RP103; dosing times/dates not recorded in patient diary.

PD=pharmacodynamics; Q3= Quarterly 3

Source: RP103-04 Interim Clinical Study Report (Amended) dated January 10, 2013

All but one of the 40 patients enrolled into RP103-04 has had at least minor protocol deviation. Minor protocol deviations included missed assessments or assessment performed outside the protocol window (32 patients), missed study drug doses (13 patients), errors in study drug dose (6 patients), errors in study drug administration (9 patients), noncompliance with study drug (2 patients), and deviations in eligibility or informed consent (2 patients).

5.3.38 Compliance

Twelve patients were reported to have missed study doses during the trial, including 7 patients who missed doses due to unavailability of RP103 (see [Table 25](#)).

Table 25: RP103-03 Patients Missing Doses of Study Drug

Patient ID	# doses missed	Visit	Comment
01004	7 days	Monthly 1	Patient ill (vomiting)
03004	1	Monthly 8	
03006	2	Quarterly 1	
03101	1	Monthly 4	
06001	Unspecified	Screening	RP103 re-supply issue
06002	Unspecified	Screening	RP103 re-supply issue
06003	13 days	Monthly 1	RP103 re-supply issue
06004	Unspecified	Screening	RP103 re-supply issue
08001	5 days	Monthly 1	RP103 unavailable
08002	5 days 18 days	Monthly 1 Monthly 2	RP103 unavailable
09001	7 days	Monthly 1	RP1003 unavailable
09004	1	Quarterly 1	

Source: RP103-04 Interim Clinical Study Report (Amended) dated January 10, 2013, Listing 16.2.2.4

Reviewer Comments:

Several patients were administered Cystagon instead of RP103 for extended periods of time during screening (3 patients), Month 1 (5 patients), and Month 2 (1 patient). I was not able to determine from the analysis datasets whether or not these substitutions coincided with PD sampling times for these patients. Thus, WBC cystine values for these patients for these time points may not reflect RP103 treatment. However, since there were no further disruptions in RP103 supply for the remainder of the trial, missed dosing did not appear to impact assessment of the long-term efficacy of RP103.

5.3.39 Review of RP103-04 Study Results

A. Demographics

The mean age of patients in the trial was 11 years (range 2 to 20 years). The mean body surface area (BSA) and daily Cystagon dose for patients in the safety population were 1.13 m² and 1.49 mg/m²/day, respectively. Mean baseline WBC cystine levels were higher in the new patients enrolled into RP103-04 (1.38 ± 0.84 nmol/½ cystine/mg protein) compared to baseline cystine levels in patients enrolled from RP103-03 (0.78 ± 0.68 nmol ½ cystine/mg protein). Mean baseline eGFR was 67 ± 24 ml/Min/1.73 m².

Table 26: RP103-04 Baseline Patient Characteristics (Safety Population)

Characteristic	Overall (n=48)
Age (years) N Mean \pm SD Median Min,Max	48 10.6 \pm 4.4 10.5 2,20
Age Cohorts (years) 2-12 13-17 18+	32 (67%) 13 (27%) 3 (6%)
Gender [n(%)] Male Female	30 (63%) 18 (37%)
Race [n(%)] Caucasian Other	47 (98%) 1 (2%)
Weight (kg) N (%) Mean \pm SD Median Min,Max	47 34.7 \pm 16.4 31.2 12.1, 90.4
BSA (m²) N (%) Mean \pm SD Median Min,Max	47 1.13 \pm 0.36 1.08 0.53, 2.08
Previous Daily Dose of Cystagon (mg/m²/day) N (%) Mean \pm SD Median Min,Max	47 1.49 \pm .35 1.46 0.79, 2.2
Total Daily RP103 Dose (Average % of Previous Cystagon Dose)* N (%) Mean \pm SD Median Min,Max	39 81.5 \pm 10.4 86.1 46.6, 105
Baseline WBC Cystine Levels (nmol ½ cystine/mg protein) N Mean \pm SD Median Min,Max	48 0.89 \pm 1.58 0.52 0.03, 10.6
Estimated Glomerular Filtration Rate (ml/min/1.73 m²) N Mean \pm SD Median Min,Max	46 67 \pm 26 62 26, 116

* Patients who completed RP103-03

Table 27: RP103-04 Baseline Patient Characteristics by Patient Subgroups (Safety Population)

Characteristic	Patients Completing RP103-03 N=40	Other RP103-04 Patients N=8	Total N=48
Age (years)			
N	40	8	48
Mean \pm SD	11.5 \pm 3.6	7.3 \pm 6.0	10.6 \pm 4.4
Median	11	5	10.5
Min,Max	6, 20	2, 20	2,20
Gender [n(%)]			
Male	23 (58%)	7 (87%)	30 (63%)
Female	17 (42%)	1(13%)	18 (37%)
BSA (m²)			
N	39	8	47
Mean \pm SD	1.19 \pm 0.3	0.90 \pm 0.46	1.13 \pm 0.36
Median	1.11	0.66	1.08
Min,Max	0.8, 2.1	0.53, 1.83	0.53, 2.08
Previous Daily Dose Cystagon (g/m²/day)			
N	39	8	47
Mean \pm SD	1.54 \pm 0.33	1.30 \pm 0.40	1.49 \pm 0.35
Median	1.52	1.25	1.46
Min,Max	0.79, 2.2	0.91, 2.12	0.79, 2.2
Baseline WBC Cystine Levels (nmol $\frac{1}{2}$ cystine/mg protein)			
N	40	8	48
Mean \pm SD	0.78 \pm 0.68	1.38 \pm 0.84	0.89 \pm 1.58
Median	0.35	1.18	0.52
Min,Max	0.03, 10.6	0.52, 3.33	0.03, 10.6

B. Review of Efficacy

Efficacy Summary

The trial results indicated that patients maintain WBC cystine <1 nmol $\frac{1}{2}$ cystine/mg protein with long-term RP103 treatment. Some patients even achieved normal or near-normal WBC cystine levels. In general, patients receiving higher doses of RP103 achieved greater reductions in WBC cystine levels; however, there was large inter-patient variability. The majority of patients with baseline elevated WBC cystine levels did not achieve reductions in WBC cystine levels <1 nmol $\frac{1}{2}$ cystine/mg protein. There appeared to be a larger treatment effect in females compared to males. There did not appear to be any evidence of patients developing tolerance to RP103.

Overall, quality of life appeared to be unchanged over the course of the trial. There was some suggestion of improvement in quality of life in the adolescent age cohort.

However, the small sample size, especially for later time points, limits the interpretation of these findings.

Overall, there did not appear to be any consistent patterns in changes in swallowing functioning. The majority of patients (91%) had no difficulty or minimal difficulty swallowing at baseline (VAS score 0 or 1).

1. Study Endpoints

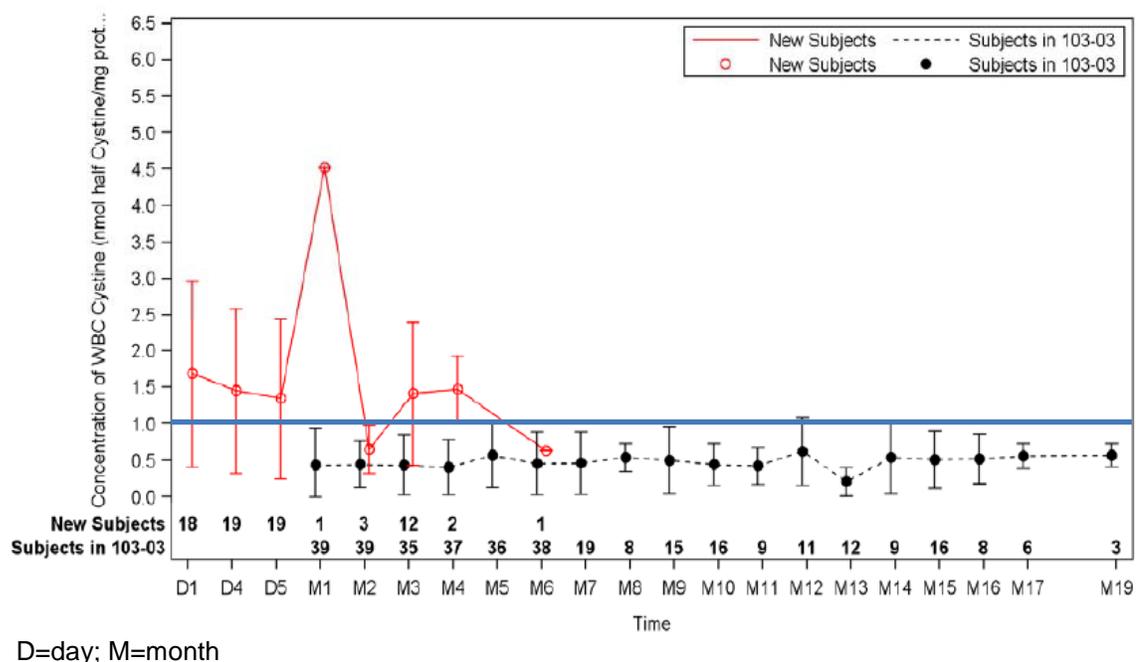
WBC Cystine Levels Over Time

As discussed earlier, WBC cystine levels were measured at monthly intervals for patients who completed RP103-03 for up to nine months as patients were transitioned into a quarterly assessment schedule. Patients who had not participated in RP103-03 were only assessed at quarterly intervals. [Figure 9](#) presents WBC cystine values over time for patients enrolled from RP103-03 (black data points in graph) and for patients newly enrolled into RP103-04 (red data points in graph).¹⁷ The mean baseline WBC cystine value for patients who completed RP103-03 was 0.67 nmol ½ cystine/mg protein. The applicant noted this value may not accurately represent the baseline value for the RP103-03 subgroup since only 21/40 RP103-03 patients (53%) had baseline WBC cystine values available. Patients who completed RP103-03 maintained WBC cystine levels below 1 nmol ½ cystine/mg protein from Month 1 up to Month 19, the last time point for which data was available. Mean WBC cystine values ranged from 0.21 nmol ½ cystine/mg protein (<0.2 is normal) to 0.62 nmol ½ cystine/mg protein. Mean WBC levels for patients newly enrolled into RP103-04 were > 1 nmol ½ cystine/mg protein during screening (n=19) and continued to be >1 nmol ½ cystine/mg protein after 3 months of treatment with RP103 (n=12). Only one newly enrolled patient had WBC cystine data at Month 6 of treatment. The applicant noted that newly enrolled patients were not required to have low WBC cystine levels at entry into the study and these patients are undergoing adjustments of their RP103 doses.

Sixteen of 48 patients (33%) had elevated WBC cystine levels (>1 nmol ½ cystine/mg protein) at one or more time points, including nine patients who had baseline elevated WBC cystine levels (3 RP103-03 patients and 6 newly enrolled patients).

¹⁷ Per the Agency's request, the applicant submitted this graph in an amended 120-Day Safety Update on January 30, 2013. The graph includes data points for all patients enrolled in RP103-04 at the time of data cut-off (June 22, 2012).

Figure 9: Mean (\pm SD) Concentration of WBC Cystine (nmol $\frac{1}{2}$ cystine/mg protein) Over Time (PK/PD Population)



Source: NDA 203389 120-Day Safety Update submitted January 30, 2013

Reviewer Comments:

Patients enrolled from RP103 appeared to maintain WBC cystine level < 1 nmol $\frac{1}{2}$ cystine/mg protein with long-term RP103 treatment. Some patients even achieved normal or near-normal WBC cystine levels (the mean WBC cystine level at Month 12 was 0.21 nmol $\frac{1}{2}$ cystine/mg protein). Patients with baseline elevated WBC cystine levels also achieved some reduction in WBC cystine levels. However, the majority of these patients did not achieve WBC cystine levels < 1 nmol $\frac{1}{2}$ cystine/mg protein. As discussed later, this difference in response may be due to differences in dosing. Patients with elevated WBC cystine levels tended to be on lower doses of RP103 (based on dose by body surface area) compared with the doses administered to patients with WBC cystine levels < 1 nmol $\frac{1}{2}$ cystine/mg protein.

Quality of Life

There were no clear patterns observed in reported quality of life. Overall, quality of life appeared to be unchanged over the course of the trial. There was some suggestion of improvement in quality of life in the adolescent age cohort. However, the small sample size, especially for later time points, limits the interpretation of these findings. [Table 28](#) summarizes quality of life scores for RP103-04.

Table 28: RP103-04 Quality of Life (PedsQL 4.0 Generic Core Scale) Scores

Age Cohort	PedsQL 4.0 Scores						
	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18
5-7 years						N=0	N=0
N	8	3	4	5	N=2		--
Mean±SD	75 ± 24	74 ± 36	77 ± 20	78 ± 17	62 ± 51		--
Median	75	91	75	70	62		--
(Min,Max)	(28, 100)	(33, 98)	(56, 100)	(63, 100)	(26, 98)		
8-12 years						N=7	N=1
N	N=13	N=5	N=9	N=5	N=6		
Mean±SD	79 ± 13	73 ± 14	85 ± 11	86 ± 9	74 ± 14	78 ± 14	89
Median	82	65	86	86	71	83	--
(Min,Max)	(50, 96)	(59, 90)	(61, 99)	(75, 99)	(61, 97)	(51, 2)	--
13-18 years						N=8	N=3
N	N=14	N=11	N=3	N=4	N=10		
Mean±SD	75 ± 13	76 ± 12	84 ± 18	86 ± 12	78 ± 14	86 ± 15	85 ± 14
Median	76	76	93	86	81	93	90
(Min,Max)	(51, 91)	(54, 95)	(64, 96)	(72, 100)	59, 95)	60, 100	68, 96

VAS Difficulty Swallowing

Overall, there did not appear to be any consistent patterns in changes in swallowing functioning. The majority of patients (39/43 patients; 91%) had no difficulty swallowing or minimal difficulty swallowing at baseline (VAS score 0 or 1). The four patients who reported higher VAS scores (VAS score ≥ 4) at baseline all reported no difficulty swallowing or minimal difficulty swallowing at later time points in the study. Seven of 43 patients with no difficulty swallowing or minimal difficulty swallowing at baseline had VAS scores ≥ 4 at one or more later time points, including 2 patients with VAS scores of 10, 1 patient with a VAS score of 6, and 4 patients with VAS scores of 4.

Table 29: RP103-04 VAS Difficulty Swallowing Score

VAS Difficulty Swallowing Score	Study Visit (N)												
	Scr (43)	M1 (38)	M2 (38)	M3 (37)	M4 (37)	M5 (37)	M6 (36)	M7 (18)	M8 (8)	Q1 (31)	Q2 (5)	Q3 (1)	End Study (2)
0	28	28	27	24	26	27	24	10	6	20	2	1	0
2	11	7	11	11	6	9	10	7	1	8	3	0	2
4	3	3	0	1	5	1	2	1	1	1	0	0	0
6	0	0	0	1	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0
10	1	0	0	0	0	0	0	0	0	2	0	0	0

2. Drug Dose Response Relationship

In general, patients receiving higher doses of RP103 achieved greater reductions in WBC cystine levels (see [Table 30](#)). However, there was large inter-patient variability, with some patients achieving low WBC cystine levels while receiving doses that were below the recommended dosing range for Cystagon and some patients with elevated WBC cystine levels while receiving doses that exceeded the recommended dosing range for Cystagon (1.3 g/m²/day to 1.95 g/m²/day).

Table 30: Mean WBC Cystine Level (nmol ½ cystine/mg protein) & Mean Total Daily Cysteamine Dose (g/m²/day) Stratified by WBC Cystine Response

Parameter	Study Visit					
	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15
WBC Cystine Level (nmol ½ cystine/ mg protein)						
Pts w/ WBC Cystine<1						
N	39	34	34	12	8	13
Mean (±SD)	0.4 (0.26)	0.38 (0.30)	0.33 (0.24)	0.32 (0.25)	0.37 (0.20)	0.35 (0.18)
Median	0.35	0.29	0.31	0.31	0.33	0.33
Min,Max	0.03, 0.96	0.03, 0.91	0, 0.85	0.04, 0.68	0.10, 0.73	0.04, 0.7
Pts w/ WBC Cystine≥1						
N	9	6	5	3	3	3
Mean (±SD)	2.79 (3.02)	1.5 (0.52)	1.36 (0.27)	1.25 (0.26)	1.29 (0.13)	1.21 (0.16)
Median	1.52	1.57	1.42	1.14	1.28	1.13
Min,Max	1.18,10.6	1.07, 2.21	1.07, 1.69	1.07,1.55	1.17, 1.42	1.1, 1.39
Total Daily Cysteamine Dose (g/m²/day)						
Pts w/ WBC Cystine<1						
N	39	34	34	12	8	13
Mean (±SD)	1.52 (0.31)	1.29 (0.24)	1.22 (0.25)	1.18 (0.35)	1.17 (0.48)	1.25 (0.35)
Median	1.50	1.28	1.2	1.11	1.05	1.29
Min,Max	0.93, 2.12	0.7, 1.84	0.7, 1.81	0.73, 2.03	0.654, 2.19	0.79, 2.12
Pts w/ WBC Cystine≥1						
N	9	6	5	3	3	3
Mean (±SD)	1.37 (0.49)	0.91 (.0.19)	1.47 (0.44)	1.13 (0.45)	0.99 (0.28)	1.11 (0.12)
Median	1.25	0.9	1.42	1.23	1.03	1.13
Min,Max	0.79, 2.2	0.63, 0.91	0.9, 1.97	0.64, 1.53	0.7, 1.23	0.98, 1.22

3. Subpopulations

There appeared to be a larger treatment effect in females compared to males. Although the mean baseline WBC cystine level was higher in females (1.07 nmol ½ cystine/mg protein) compared to males (0.8 nmol ½ cystine/mg protein), mean WBC cystine levels were lower over time for females compared to males with RP103 treatment at a mean dose similar to or lower than the mean dose for males. For females, mean cystine levels from Month 3 to Month 15 ranged from 0.32 nmol ½ cystine/mg protein to 0.44 nmol ½ cystine/mg protein, and mean RP103 doses ranged from 1.0 g/m²/day to 1.3 g/m²/day. For males, mean cystine levels from Month 3 to Month 15 ranged from 0.53 nmol ½ cystine/mg protein to 0.78 nmol ½ cystine/mg protein, and mean RP103 doses

ranged from 1.2 g/m²/day to 1.4 g/m²/day. [Table 31](#) summarizes WBC cystine levels and total daily RP103 dose by gender from baseline to Month 15.

Table 31: RP103-04 WBC Cystine Levels (nmol ½ cystine/mg protein) & Total Daily RP103 Dose (g/ m²/day) Over Time by Gender

Parameter	Study Visit					
	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15
WBC Cystine Level (nmol ½ cystine/ mg protein)						
Males						
N	29	24	23	9	6	8
Mean (±SD)	0.80 (0.78)	0.68 (0.63)	0.53 (0.44)	0.59 (0.50)	0.78 (0.47)	0.69 (0.44)
Median	0.51	0.61	0.46	0.59	0.65	0.50
Min,Max	0.05, 3.33	0.03, 2.21	0.01, 1.69	0.06, 1.55	0.25, 1.42	0.29, 1.39
Females						
N	18	15	16	6	5	8
Mean (±SD)	1.07 (2.41)	0.40 (0.36)	0.36 (0.39)	0.37 (0.40)	0.44 (0.42)	0.32 (0.22)
Median	0.44	0.23	0.31	0.28	0.29	0.34
Min,Max	0.03, 10.6	0.05, 1.17	0, 1.54	0.04, 1.07	0.1, 1.17	0.04, 0.7
Total daily RP103 dose (g/m²/day)						
Males						
N	22	24	23	9	6	7
Mean (±SD)	1.28 (0.29)	1.25 (0.27)	1.28 (0.31)	1.38 (0.41)	1.22 (0.49)	1.21 (0.25)
Median	1.23	1.22	1.21	1.44	1.05	1.16
Min,Max	0.83, 1.92	0.87, 1.84	0.83, 1.97	0.92, 2.16	0.82, 2.19	0.98, 1.6
Females						
N	18	15	15	6	5	8
Mean (±SD)	1.17 (0.30)	1.18 (0.29)	1.21 (0.25)	1.34 (0.26)	1.01 (0.34)	1.29 (0.26)
Median	1.25	1.27	1.25	1.28	1.02	1.28
Min,Max	0.56, 1.55	0.57, 1.57	0.7, 1.54	1.09, 1.65	0.64, 1.44	0.98, 1.6

4. Discussion of Persistence of Efficacy and/or Tolerance Effects

As noted earlier, patients appeared to achieve and maintain WBC cystine levels well below the therapeutic target of < 1 nmol ½ cystine/mg protein, with some patients achieving normal or near normal WBC cystine levels. There did not appear to be any evidence of patients developing tolerance to RP103.

6 Review of Efficacy

6.1 Indication

The applicant proposes the following indication:

“PROCYSBI (cysteamine bitartrate) delayed-release capsules is a cystine-depleting (b) (4) indicated for the management of nephropathic cystinosis in children and adults.”

Although RP103 was not evaluated in treatment-naïve patients, I consider an indication for this population to be acceptable since the applicant has demonstrated non-inferiority and the safety profile of RP103 appears to be similar to Cystagon in patients 6 years and older. However, no efficacy data for children under six years old are currently available for this product. Therefore, the indication should be limited to patients 6 years and older. Therefore, I recommend that the indication be revised as follows:

“PROCYSBI (cysteamine bitartrate) delayed-release capsules is a cystine-depleting (b) (4) indicated for the management of nephropathic cystinosis in children age 6 years and older and adults.”

For a final version of the indication for PROCYSBI, please see final product labeling.

Efficacy is discussed in [Section 5](#) of this review.

7 Review of Safety

Safety Summary

RP103 is generally well tolerated in pediatric patients 6 years and older and adult patients with nephropathic cystinosis who were previously treated with Cystagon. There were no deaths in any of the clinical trials. Additionally, only two of the 26 serious adverse events (SAEs) appear to be directly related to treatment with RP103 (abdominal discomfort and constipation); all other SAEs were assessed as not being treatment-related.

The most common AEs ($\geq 5\%$) reported in bioequivalence trials and in trials in patients with nephropathic cystinosis were abdominal pain, nausea, vomiting, headaches, and dizziness. Adverse reactions considered related to the use of RP103 as reported by the applicant include abdominal pain, nausea, vomiting, diarrhea, headache, dizziness, breath odor, body odor, decreased appetite, anaphylaxis/allergic reaction, renal impairment, skin rash, and fatigue.

For the pivotal trial (RP103-03), the applicant reported an almost 2-fold difference in the overall incidence of AEs and the incidence of treatment-related AEs for the RP103 treatment period (58% overall AE incidence and 15 percent treatment-related AE incidence) and the Cystagon treatment period (32% overall AE incidence and 15 percent treatment-related AE incidence). These differences appeared to be due primarily to higher incidences of gastrointestinal AEs during the RP103 treatment period. The applicant postulated that restriction of PPI use during the RP103 treatment period likely contributed to these findings.

For the extension trial (RP103-04), the applicant reported that 25/60 (42%) patients in experienced events considered to be related to the use of RP103. Based on my independent analysis of reported adverse events, 1/72 (1.4%) individuals in the safety database experienced an anaphylactic reaction. I was not able to comprehensively analyze safety data for RP103-04 since only top-line safety data were available for the full RP103-04 safety population. However, based on review of the safety data available for this review cycle, my independent safety analysis did not uncover major discrepancies compared with the applicant's analysis.

Overall, the safety profile of RP103 appears to be similar to the reference product Cystagon, although a higher incidence of gastrointestinal adverse events were observed in the pivotal trial with RP103 compared to Cystagon. Due to the similarity in safety, in this reviewer's opinion, the data appear adequate to support an indication in treatment-naïve patients as well as patients previously treated with Cystagon. However, safety data were not available for pediatric patients under 6 years old. The applicant has submitted a Proposed Pediatric Study Request (PPSR) [REDACTED] (b) (4)

(b) (4)

(b) (4) Therefore, the Division will present a Written Request to the Pediatric Review Committee (b) (4)

The applicant submitted a proposed pharmacovigilance plan for RP103. In addition to routine pharmacovigilance and product labeling, proposed risk minimization activities include heightened monitoring to address potential risks (i.e., Ehler-Danlos like syndrome and fibrosing colonopathy) and a Medication Guide. In this reviewer's opinion, routine pharmacovigilance activities are sufficient to minimize risks for treatment with RP103.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety information for this clinical review includes complete study data from all clinical trials except for RP103-04, for which interim safety data were submitted. The interim clinical study report for RP203-04 includes safety data on 48 patients. In addition, the 120-Day Safety Update contains top-line safety data for the full RP103-04 safety population (60 patients). The database cut-off date for the interim safety data was June 22, 2012.

Reviewer Comment:

Because only top-line safety data were available for the full RP103-04 population, I was not able to do a comprehensive analysis of the data for patients (n=12) enrolled into the trial after the application submission. However, the available data appeared to be adequate to assess for safety.

7.1.2 Categorization of Adverse Events

The applicant coded AEs by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). I revised AE preferred terms and SOC terms so that AE terms were clustered together to allow for a more meaningful description of the AE profile of cysteamine bitartrate. For example, abdominal pain and abdominal discomfort were grouped together.

Reporting of adverse events included information such as classification of AE using standard medical terminology (MedDRA Version 13.0), system organ class (SOC), timing of AE in relationship to administration of study drug, classification of relationship

to study medication, classification of severity of AE, and date of onset and resolution of AE. These appear to be adequate to assess the safety profile of cysteamine bitartrate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Due to differences in the study populations, the type and quality of data collected, and the duration of data collection, I reviewed pooled safety data for the bioequivalence studies in healthy volunteers separately from pooled safety data for patients with nephropathic cystinosis.

7.2 Adequacy of Safety Assessments

Safety parameters for clinical studies and trials reviewed included physical examination, vital signs, ECG, clinical chemistry, hematology, and urinalysis, and adverse events. In addition, renal function (measured by estimated glomerular filtration rate [eGFR]) was monitored in RP103-04 patients. These safety parameters appear to be adequate to assess the safety profile of RP103.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety database includes 40 healthy volunteers and 72 patients with nephropathic cystinosis who were previously treated with Cystagon. Healthy volunteers received a single 600 mg dose of RP103. Total daily RP103 dosing in patients ranged from 0.5 g/m²/day to 2.23 g/m²/day. With the exception of patients enrolled in RP103-04, the duration of exposure for trial participants was less than one month. As of June 22, 2012, 37 patients enrolled in RP103-04 had completed at least 10 months of treatment with RP103 and 3 patients had completed at least 20 months of treatment (see [Table 32](#)).

Table 32: Summary of Duration of Exposure to RP103 (RP103-04 Safety Population)

Duration of Exposure to RP103	RP103-04 (n=60)
<1 month	3
≥1 month	57
≥5 months	43
≥10 months	37
≥15 months	27
≥20 months	3

[Table 33](#) summarizes the demographic data for healthy volunteers and patients with nephropathic cystinosis. The demographic data for the three trials in healthy volunteers

were similar. There were some demographic differences between the study populations for the three trials in patients. Patients enrolled in RP103-04 were slightly younger (mean age was 11 years) than patients enrolled in RP103-01 and RP103-03 (mean age was 13 years and 12 years, respectively). There was a higher proportion of males enrolled in RP103-01 and RP103-04 (78% males and 62% males, respectively) compared to RP103-03 (56% males). The trials did not include standard assessments of disease-specific clinical parameters (e.g., renal function, growth, corneal disease, etc.), with the exception of eGFR safety assessment in RP103-04. Therefore, there were insufficient data to assess for similarities or differences in clinical status between the trial populations for RP103-01, RP103-03, and RP103-04.

Table 33: Baseline Demographics for RP103 Safety Population

Parameter	Trial Population					
	Nephropathic Cystinosis Patients			Healthy Volunteers		
	RP103-01 N=9	RP103-03 N=43	RP103-04 N=60	RP103-02 N=18	RP103-05 N=20	RP103-06 N=20
Age (yrs) Mean±SD (Min,Max)	12.8 ± 4.8 (7, 24)	11.7 ± 4.2 (6, 26)	10.7 ± 6.1 (2, 32)	30.9 ± 12.6 (20, 59)	37.5 ± 12.5 (19, 64)	33.3 ± 10.8 (19, 55)
Sex						
Male	7 (78%)	24 (56%)	37 (62%)	14 (78%)	13 (65%)	10 (50%)
Female	2 (22%)	19 (44%)	23 (38%)	4 (22%)	7 (35%)	10 (50%)
Race						
White	8 (89%)	42 (98%)	59 (98%)	15 (83%)	18 (90%)	1 (5%)
Black	1(11%)	1 (2%)	0	3 (17%)	2 (10%)	17 (85%)
Other	0	0	1 (2%)	0	0	2(10%)
Weight (kg) Mean±SD (Min,Max)	36.8 ± 9.2 (21, 51)	36.0 ± 14.2 (19, 89)	33.4 ± 17.3^a (10, 90) ^b	76.7 ± 11.3 (57, 103)	72.7 ± 12.7 (55, 105)	73.0 ± 13.0 (59, 98)
BSA (m²) Mean±SD (Min,Max)	1.2 ± 0.2 (0.8, 1.4)	1.2 ± 0.3 (0.8, 2.1)	1.1 ± 0.4^b (0.5, 2.1)	1.9 ± 0.2 (1.7, 2.3)	1.9 ± 0.2 (1.6, 2.4)	1.9 ± 0.2 (1.6, 2.3)

^aN=59; ^bN=58

7.2.2 Explorations for Dose Response

Relationship between dose response and safety was evaluated in RP103-04. No clear dose response relationship in terms of safety signals was observed in the trial. See Section 7.5.1 for evaluation of AEs and various dosages of cysteamine bitartrate treatment.

7.2.5 Metabolic, Clearance, and Interaction Workup

The results of metabolism and transporter studies submitted by the applicant are summarized in [Section 4.4.4](#). The applicant noted that RP103 is a substrate but not an inhibitor of the uptake transport OCT2. Other OCT2 substrates included GAR medications commonly used by patients with nephropathic cystinosis (including cimetidine, famotidine, and ranitidine). (b) (4)

[REDACTED]

7.2.4 Routine Clinical Testing

Routine safety laboratory studies were performed for all RP103 trials. Safety laboratory studies were performed by laboratories at the individual study sites for RP103-01 and the bioavailability/bioequivalence studies. Safety laboratory studies were performed at a central laboratory for RP103-03 and RP1-03-04, except for pregnancy testing which was performed at local laboratory sites. Laboratory results are discussed in [Section 7.4.2](#).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adequate evaluation for potential adverse events for cysteamine bitartrate was performed through a literature search by the applicant. The literature review included published data on adverse events reported in patients treated long-term with cysteamine and adverse events associated with high doses of cysteamine. The most commonly reported events in the literature include gastrointestinal upset (nausea, vomiting, abdominal pain, and diarrhea) and halitosis. In a recent article reviewing long-term cysteamine treatment in adolescents and adults, the authors point to these side effects as significant contributors to poor patient compliance with cysteamine treatment.¹⁸ Development of skin, vascular, neurologic, muscular, and bone lesions has been reported following administration of high doses of cysteamine (doses >1.95 g/m²/day). These include skin and bone lesions resembling clinical findings in patients with Ehler-Danlos syndrome.¹⁹

7.3 Major Safety Results

The major safety results reviewed in this section are from all RP103 clinical trials. The results include safety data reported in the 120-Day Safety Update submitted on January 30, 2013.

¹⁸ Brodin-Sartorius A, Tête M-J et al, Cystamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, *Kidney Int* 2011 81(2): 179-189.

¹⁹ Besouw MTP, Bowker R, Cysteamine toxicity in patients with cystinosis, *J Pediatr* 2011; 159(6): 1004-1011.

7.3.1 Deaths

No deaths have been reported in this development program to date.

7.3.2 Nonfatal Serious Adverse Events

A total of 26 SAEs have been reporting for 19 individuals treated with RP103, including seven SAEs in 7/43 (16%) patients enrolled in RP103-03 and 19 SAEs in 13/60 (22%) patients enrolled in RP103-04 (one patient [07002] experienced SAEs in both RP103-03 and RP103-04). No SAEs were reported for RP103-01, RP103-02, RP103-05, and RP103-06.

Of the seven RP103-03 patients that experienced a SAE, one patient experienced an SAE while receiving Cystagon. Of the 13 RP103-04 patients enrolled in RP104 that experienced a SAE, three patients experienced more than one SAE (patients 02010, 07002, and 07003).

Two patients experienced SAEs that were assessed as treatment-related, including one patient in RP103-03 who experienced abdominal discomfort and one patient in RP103-04 who experienced constipation; all other SAEs were assessed as not being treatment-related. [Table 34](#) lists the specific serious adverse events reported in the clinical trials for cysteamine bitartrate.

Table 34: Summary of Serious Adverse Events in RP103 Trials

	RP103-01	RP103-02	RP103-03	RP103-04	RP103-05	RP103-06
# of Patients	0/9	0/18	7/43 (16%)	13/60 (22%)	0/20	0/20
# of SAEs	0	0	7	19	0	0
Events			Abdominal discomfort Femur fracture Gastroenteritis Hypokalemia Hypovolemia Knee deformity Vomiting	Anemia Appendicitis (2 events) Alcohol poisoning Chronic otitis media Constipation Cryptorchism Diarrhea Gastric fistula Gastroenteritis (3 events) Hypocalcemia (2 events) Knee deformity (2 events) Mental disorder Pseudoparalysis Renal failure		

Narratives for the reported SAEs:

Patient 06003 (RP103-03)

SAE: Abdominal discomfort

The patient is a 9 year-old male with a medical history significant for photophobia, hypothyroidism, and cow's milk protein allergy. Concomitant medications included dexchlorpheniramine, levothyroxine, potassium supplements, levocarnitine, phosphorus supplements, and alfacalcidol. The patient experienced severe abdominal pain and malaise within one hour of receiving his first dose of RP103. His symptoms progressed after the second and third doses to gastric intolerance and resulted in the patient being hospitalized for dehydration. The patient's hospital course was significant for hypokalemia (potassium 2.5 nmol/L) which resolved after treatment with oral potassium. RP103 dosing was suspending for three days with resolution of the patient's abdominal symptoms. The patient tolerated restarting RP103 along with domperidone and phloroglucinal hydrate and was discharged home.

The investigator assessed the reported event as possibly related to RP103. The applicant concurred with this assessment.

Comment: This reviewer agrees that the event appears to be treatment-related.

Patient 07001 (RP103-03)

SAE: Vomiting

The patient is a 7 year-old male who experienced several episodes of vomiting over a 6-day period. Concomitant medications included levocarnil, phosphorus, sodium bicarbonate, indomethacin, potassium bicarbonate, vitamin D, somatropin, and omeprazole. The first episode of vomiting occurred two days after the patient started treatment with RP103. The vomiting episodes were not associated with headache, abdominal pain, diarrhea, fever or other symptoms. The patient was hospitalized for one day for monitoring. He had a normal abdominal exam and no signs of dehydration upon admission. The patient had 2 episodes of vomiting during the hospital admission. Laboratory evaluations were significant for decreased bicarbonate and elevated creatinine levels (14 nmol/L and 64 μ mol/L, respectively) and normal liver function tests. A work-up for infection (urine cultures and Epstein-Barr and cytomegalovirus serology tests) was negative).

The investigator assessed the reported event as unrelated to RP103. The applicant concurred with this assessment, noting that an acquired infection was a "reasonable alternative etiology."

Comment: In this reviewer's opinion, this event should be considered as possibly treatment related, based on the timing of the onset of symptoms. Gastrointestinal symptoms, including nausea, vomiting anorexia, and abdominal pain, are labeled side effects of cysteamine therapy. There is insufficient information to support the applicant's

speculation that the vomiting was due to an acquired infection. Although some pediatric infections may present initially with vomiting (e.g., viral gastroenteritis) in the absence of other signs or symptoms, isolated vomiting is uncommon. No information was provided on whether any patient contacts had been ill; a positive history of ill contacts would be supportive of an infectious etiology.

Patient 01002 (RP103-03)

SAE: Knee deformity (genu valgum)

The patient is a 12 year-old female with a history of genu valgum and photophobia. Concomitant medications include potassium supplements, levocarnitine, and sodium bicarbonate. On [REDACTED] (b) (6) five days after starting RP103 treatment, the patient was hospitalized for elective knee surgery (bilateral osteotomy for genu valgum). The patient had an uncomplicated post-operative course and was discharged home on [REDACTED] (b) (6). The patient's family decided to withdraw the patient from the study following her surgery and also withdrew her sibling at the same time. The patient has been lost to follow-up.

The investigator assessed the reported event as not related to treatment with RP103. The applicant concurred with this assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 01005 (RP103-03)

SAE: Hypovolemia

The patient is a 26 year-old female with a history of diarrhea, hypokalemia, carnitine deficiency, and Raynaud's syndrome. Concomitant medications included chlorothiazide, potassium hydrochloride, citrate, levocarnitine, phosphorus supplements, progesterone-estrogen, nifedipine, and omeprazole. The patient was treated RP103 (2.4 grams daily) for 21 days and then resumed treatment with Cystagon (3 grams daily). On April 10, 2011, one day after restarting Cystagon, the patient experienced vomiting and did not take her study medication (number of missed doses was unspecified). On [REDACTED] (b) (6) the patient reported nausea and increased vomiting and was noted to be afebrile with tachycardia, hypertensive, and anorexic on exam during a clinic visit. The report states that the patient had taken Cystagon that day. She was hospitalized for observation and rehydration. The patient's blood pressure normalized and the vomiting resolved after rehydration. The patient was discharged on [REDACTED] (b) (6).

The investigator assessed the reported event of hypovolemia as being secondary to vomiting and unrelated to treatment with Cystagon. The applicant concurred with this assessment.

Comment: It is unclear whether or not this event was treatment-related. As noted earlier, gastrointestinal symptoms such as vomiting are a labeled side effect of Cystagon treatment. The investigator and applicant acknowledge that the patient's hypovolemia was secondary to vomiting but assert that the vomiting was not related to treatment. The narrative did not provide information on the specific time of the last dose of Cystagon prior to the onset of vomiting. In addition, the narrative does not provide information on whether the patient was evaluated for other etiologies for vomiting.

Patient 03008 (RP103-03)

SAE: Gastroenteritis

The patient is a 6 year-old female with Fanconi's syndrome, photophobia, intermittent emesis, hypercholesterolemia, and intermittent headaches. Concomitant medications included Cystagon, potassium, sodium phosphate, ferrous sulfate, multivitamin, levocarnitine, pravastatin, calcitriol, and phosphorus.

The patient was treated with Cystagon (1000 mg) for 21 days and then started on RP103 (900 mg). On May 23, 2011, 19 days after starting RP103, the patient experienced gastroenteritis and was noted to be tired and lethargic during a study visit. On [REDACTED] (b) (6) the patient presented to the emergency department (ED) with vomiting and diarrhea. The patient was treated in the ED for dehydration, hypokalemia, and a possible urine infection and admitted briefly for further monitoring. The patient improved and was able to be discharged later the same day on an oral antibiotic (cephalexin). The patient was noted to be healthy at a follow-up visit on May 26, 2011. The antibiotic was discontinued due to a negative urine culture.

The investigator assessed the event of gastroenteritis as being unrelated to treatment. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 06004 (RP103-03)

SAE: Hypokalemia

The patient is an 11 year-old female with a history of photophobia, left foot metatarsal fracture, and scoliosis. Concomitant medications included potassium supplements, enalapril, omeprazole, potassium bicarbonate, calcium, glucose-1-phosphate disodium tetrahydrate, alfacalcidol, calcidiol monohydrate, and sodium bicarbonate. On [REDACTED] (b) (6), twenty-one days after starting treatment with RP103, the patient presented with severe asthenia during a study visit. Study laboratory assessments revealed hypokalemia (potassium 2.5 nmol/L) and the patient subsequently was hospitalized for monitoring. The patient was treated with potassium with resolution of

the event and discharged on [REDACTED] (b) (6). The event was attributed to the patient not taking her potassium supplements for about 24 hours due to abdominal pain.

The investigator assessed the reported event as not related to treatment with RP103. The applicant concurred with this assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 07002 (RP103-03)

SAE: Femur fracture

The patient is a 16 year-old female with a history of genu valgum and internal femoral and tibial epiphyseal diaphyses with bilateral plates in May 2009. Concomitant medications included sodium bicarbonate, potassium bicarbonate, indomethacin, levocarnil, phosphorus, levothyroxine, alfacalcidol, somatropin, cysteamine, and omeprazole. On [REDACTED] (b) (6) the patient experienced a right cervical femoral fracture 13 days after her first dose of RP103 that required hospitalization for surgical repair. The patient sustained the fracture after falling from a standing position. The patient underwent osteosynthesis with placement of transcervical screws. Her post-operative course was significant for dehydration, hypokalemia, and functional renal insufficiency that resolved prior to discharge. The patient was discharged after 10 days and was scheduled for follow-up bone mineral density testing and scintigraphy. The patient also experienced SAEs in RP103-04 (see later narrative for [Patient 07002](#)).

The investigator assessed the reported event as related to underlying disease exacerbated by trauma. The applicant concurred with this assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 01001 (RP103-04)

SAE: Knee deformity (genu valgum)

The patient is a 16 year-old female with a history of genu valgum, hyperlipidemia, strabismus, pneumonia, intermittent metabolic acidosis, hypokalemia, photophobia, lethargy, somnolence, nausea, vomiting, and anorexia. Concomitant medications included potassium chloride, ondansetron, vitamin D, and calcium.

The patient completed RP103-03 and immediately started RP103-04. On [REDACTED] (b) (6) 60 days after starting RP103 treatment in RP103-04, the patient was hospitalized for elective knee surgery (osteotomy). She had an uncomplicated post-operative course and was discharged on [REDACTED] (b) (6). One dose of RP103 was withheld on the morning of surgery and dosing was resumed that evening.

The investigator assessed the event as being unrelated to treatment. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 01004 (RP103-04)

SAE: Cryptorchism

The patient is an 11 year-old male with a history of undescended testicle, carnitine deficiency, metabolic acidosis, short stature, astigmatism, photophobia, gastrostomy tube, and nausea. Concomitant medications included levocarnitine, citrate combination and somatropin.

The patient completed RP103-03 and immediately entered RP103-04. On (b) (6) approximately 5 months after starting RP103, the patient was hospitalized for one day for elective surgical repair of an undescended testicle.

The investigator assessed the event as not related to treatment with RP103. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 02010 (RP103-04)

The patient is an 11 year-old male with a history of anemia, Fanconi's syndrome, photophobia, attention deficit hyperactivity disorder, hypothyroidism, proteinuria, short stature syndrome, and gastric acid reflux. Concomitant medications include citric acid/potassium citrate/sodium citrate, levothyroxine, epoetin alfa, iron sulfate, levocarnitine, somatotropin, omeprazole, candesartan, vitamin D, and cysteamine ophthalmic drops.

The patient completed RP103-03 and immediately entered RP103-04. The patient experienced two SAEs during RP10304:

SAE: Anemia

On (b) (6) approximately four and a half months after starting RP103-04, the patient presented with lethargy and was hospitalized for anemia. The patient is reported to have had a viral-like illness for several days. His hemoglobin level at admission was 6.1 g/dL, which was a decrease from a level of 12 g/dL from six weeks prior. The patient's baseline hemoglobin at the start of RP103-03 had been 9/4 g/dL. He received a blood transfusion and was restarted on epoetin alfa therapy, which had been discontinued a few months prior to the event. The patient's hemoglobin improved post-transfusion and he was discharged on (b) (6)

The investigator assessed the event as being related to the patient's underlying disease. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

SAE: Gastroenteritis

On [REDACTED] (b) (6) approximately five months after starting RP103-04, the patient presented with a history of poor oral intake and vomiting to the emergency department. In the ED, he also experienced diarrhea and was noted to be hypotensive (BP 63/32 mmHg) on examination. He admitted to the hospital and was rehydrated intravenously until he was able to tolerate an oral diet. He was discharged home on [REDACTED] (b) (6)

The investigator assessed the event of gastroenteritis as not related to treatment with RP103. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient 02011 (RP103-04)

SAE: Constipation

The patient is a 12 year-old female with a history of acid reflux, gastronomy tube, and Nissen fundoplication. Concomitant medications included cysteamine drops and ferrous sulfate. Approximately 13 months after starting treating with RP103, the patient was hospitalized for evaluation of severe epigastric pain which had been present for one month. Prior to admission, she had undergone a complete bowel cleanout and had been started on omeprazole with some improvement in the pain. Diagnostic evaluations prior to admission were negative for H. pylori infection, celiac disease, or obstruction. Additional diagnostic evaluations performed during the hospitalization confirmed the diagnosis of constipation and the patient was discharged home after treatment with polyethylene glycol and intravenous hydration.

The investigator and the applicant assessed the abdominal pain as possibly related to RP103.

Comment: This reviewer agrees that the event appears to be treatment-related.

Patient: 03004 (RP103-04)

SAE: End stage renal disease

The patient is a 14 year-old male with a history of Stage III chronic kidney disease, Fanconi's syndrome, renal anemia, secondary hyperparathyroidism, attention deficit hyperactivity disorder, photophobia, gastric hyperacidity, gastric ulcer, short stature, nausea and vomiting, and somnolence. Concomitant medications included omeprazole,

iron, cysteamine ophthalmic drops, dexmethylphenidate, methylphenidate, potassium citrate, growth hormone, calcitriol, carnitine, clonidine, and somatropin.

The patient began treatment with RP103 on October 21, 2010. He had been on a renal transplant list since the fall of 2011 and was hospitalized on [REDACTED] (b) (6) to undergo renal transplantation. His post-operative course was significant for an allergic reaction (blistering rash) to mycophenolate mofetil. He was switched to an immunosuppression regimen of anti-thymocyte globulin, steroids, tacrolimus, and azathioprine. He was discharged on [REDACTED] (b) (6).

The investigator assessed the event of renal transplant as most likely being related to the patient's underlying disease. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient: 03101 (RP103-04)

SAE: Gastrocutaneous fistula

The patient is a 7 year-old female with a history of Fanconi syndrome, renal tubular acidosis, gastritis, gastrostomy tube placement in 2005, intermittent nausea secondary to Cystagon treatment, intermittent vomiting, anorexia, leg pain, and photophobia. Concomitant medications included citric acid with potassium and sodium citrate, lansoprazole, levocarnitine, metoclopramide, potassium phosphate, ergocalciferol, calcitriol, and potassium chloride. The patient completed RP103-03 and immediately started RP103-04.

On [REDACTED] (b) (6) 39 days after entering RP103-04, the patient experienced leakage from a gastrocutaneous fistula following removed of her gastrostomy tube. The leakage continued periodically and the patient underwent elective surgical closure of the fistula on [REDACTED] (b) (6). The patient was discharged on [REDACTED] (b) (6).

The investigator assessed the gastrocutaneous fistula as not related to RP103 treatment. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the events do not appear to be treatment-related.

Patient: 04302 (RP103-04)

SAE: Appendicitis

The patient is a 10 year-old female with a history of chronic otitis media, Fanconi syndrome, gastrostomy tube, bilateral knee surgery, Arnold-Chiari Type 1 malformation, hypothyroidism, hypocalcemia, proteinuria, and anemia. Concomitant medications included levocarnitine, phosphorus supplements, sodium bicarbonate, enalapril,

calcium, and vitamin D. The patient completed RP103-03 and immediately entered into RP103-04.

On [REDACTED] (b) (6) approximated 10 months after starting RP103, the patient was hospitalized for Grade 4 appendicitis. The patient recovered and was discharged on [REDACTED] (b) (6)

The investigator assessed the event as not related to RP103 treatment. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the events do not appear to be treatment-related.

Patient: 06001 (RP103-04)

SAE: Appendicitis

The patient is a 13 year-old male with a history of asthma, photophobia, and genu valgum. Concomitant medications included sodium chloride, potassium bicarbonate, somatotropin, analapril, calcium carbonate, indomethacin, calcifediol, alfacalcidol, and glucose-1-phosphate disodium tetrahydrate. On [REDACTED] (b) (6) he presented with abdominal pain and fever and was hospitalized. He was diagnosed with appendicitis and underwent an appendectomy. He was discharged on [REDACTED] (b) (6)

The investigator assessed the event of appendicitis as being unrelated to treatment. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient: 06006 (RP103-04)

SAE: Diarrhea

The patient is an 11 year-old male. Concomitant medications included alfacalcidol, vitamin D, phocytan, sodium bicarbonate, potassium bicarbonate, indomethacin, ferrous sulfate, omeprazole, cetirizine, ibuprofen, and loperamide. The patient completed RP103-03 and immediately entered into RP103-04.

The patient began treatment with RP103 319 days prior to the reported event of diarrhea. The patient presented with chronic diarrhea (7-10 loose or liquid, non-bloody stools per day) that began on November 25, 201. The diarrhea was not associated with fever, rash, or other abdominal symptoms and there was no history of travel. On November 28, 2011, the patient was started on loperamide. Bacterial stool cultures and parasitology testing at that time were negative. On [REDACTED] (b) (6), the patient was hospitalized for further evaluation. Diagnostic testing was negative, including stool fungal cultures, *Clostridium difficile* toxin, viral studies, and abdominal x-ray and ultrasound. The patient did not experience diarrhea during the hospitalization and was discharged on [REDACTED] (b) (6). Following discharge, the patient continued to

experience “non-serious” diarrhea until January 5, 2011. On January 4, 2011, the patient discontinued ferrous sulfate, which he had taken since January 2004.

The investigator attributed the event of diarrhea as possibly related to treatment with RP103. The applicant acknowledged that diarrhea has been observed with treatment with RP103.

Comment: This reviewer agrees with the investigator’s and applicant’s assessments.

Patient: 07002 (RP103-04)

The patient is an 18 year-old female with a history of genu valgum and tibial epiphysiodesis. Concomitant medications included sodium bicarbonate, potassium bicarbonate, levocarnil, phosphorus, levothyroxine, and alfacalcidol. The patient completed RP103-03 and immediately entered into RP103-04. The patient experienced five SAEs during RP103-04 (paralysis, acute alcohol intoxication, psychological disorder, and two events of hypocalcemia). She also experienced one SAE (femoral neck fracture) during RP103-03 (see earlier narrative for [Patient 07002](#)).

SAE: Paralysis

On [REDACTED] (b) (6) one year after beginning RP103 treatment, the patient developed general paralysis and was hospitalized. The patient reported experiencing weakness of the lower limbs and cramping, with an onset of symptoms two days prior to admission. The patient reportedly had been non-compliant with all of her medications and had discontinued RP103 prior to the event. The admission physical examination was significant for generalized muscle weakness with normal cranial nerve function and tendon reflexes. Admission laboratory results were significant for hypophosphatemia and hypokalemia. The patient was treated with potassium and phosphate supplementation with resolution of the paralysis and she was discharged on [REDACTED] (b) (6)

The investigator attributed the event of paralysis to underlying disease and inadequate potassium replacement therapy. The applicant concurred with the investigator’s assessment.

SAE: Hypocalcemia

SAE: Psychological disorder

On [REDACTED] (b) (6), approximately 17 months after starting RP103, the patient was hospitalized due to Grade 4 hypocalcemia resulting from non-compliance with calcium and vitamin D. The event was resolved on [REDACTED] (b) (6) but the patient remained hospitalized for psychological management of her noncompliance with treatment until [REDACTED] (b) (6). The investigator and applicant assessed the events of hypocalcemia and psychological disorder as not related to treatment with RP103.

SAE: Acute alcohol intoxication

On [REDACTED] (b) (6) at 20:25 p.m., the patient was hospitalized due to acute alcohol intoxication. The patient was discovered by school personnel to be drinking alcohol at 11:00 a.m. that day and was brought by emergency medical services to the emergency department. The patient was admitted for monitoring and hydration and was discharged on [REDACTED] (b) (6). The investigator and applicant assessed the event of alcohol intoxication as not related to treatment with RP103.

SAE: Hypocalcemia

On [REDACTED] (b) (6), approximately 17 months after starting RP103, the patient was hospitalized for Grade 3 hypocalcemia due to noncompliance with calcium and vitamin D supplements. She recovered from this event and was discharged on [REDACTED] (b) (6). The investigator and applicant assessed the event of alcohol intoxication as not related to treatment with RP103.

Comment: This reviewer agrees that none of the events reported for this patient appear to be treatment-related.

Patient: 07003 (RP103-04)

The patient is an 8 year-old female. Concomitant medications included indomethacin, phosphorus, potassium chloride, potassium bicarbonate, levocarnitine, and cysteamine ophthalmic drops. The patient experienced two SAEs during RP103-04:

SAE: Gastroenteritis (Episode 1)

On [REDACTED] (b) (6) approximately six months after entering RP103-04, the patient presented to the hospital with a one-day history of acute diarrhea and vomiting. The patient's father had been experiencing similar symptoms. The patient's admission examination was significant for tachycardia (heart rate 119) and slight abdominal tenderness. Diagnostic examinations were significant for stool cultures positive for *Campylobacter jejuni*. Hospital treatment included hydration and initiation of azithromycin treatment. The patient was discharged on [REDACTED] (b) (6) with continued moderate diarrhea.

SAE: Gastroenteritis (Episode 2)

On [REDACTED] (b) (6), the patient was readmitted due to a recurrence of diarrhea, cramping, and fatigue for monitoring. She did not require hydration therapy and was continued on her course of azithromycin for *Campylobacter jejuni* gastroenteritis. She was discharged the following day.

The investigator assessed both events of gastroenteritis as not related to RP103 treatment. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the events do not appear to be treatment-related.

Patient: 07004 (RP103-04)

SAE: Genu valgum

The patient is a 15 year-old female with a history of genu valgum, two prior osteotomies of the femur, and hypothyroidism. Concomitant medications included levothyroxine, phosphorus, alfacalcidol, and cysteamine ophthalmic drops. The patient completed RP103-03 and immediately entered into RP103-04.

On [REDACTED] (b) (6) approximately 10 months after starting treatment with RP103, the patient was hospitalized for corrective surgery (supracondylar femoral extension osteotomy) for pre-existing genu valgum. The patient was discharged on [REDACTED] (b) (6) and scheduled for a follow-up in six weeks.

The investigator assessed the event as not related to RP103 treatment. The applicant concurred with the investigator's assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

Patient: 07006 (RP103-04)

SAE: Chronic otitis media

The patient is a 6 year-old female with a history of chronic otitis media, rickets and growth hormone deficiency. Concomitant medications included lansoprazole, indomethacin, phosphorus supplements, sodium bicarbonate, potassium bicarbonate, sodium chloride, potassium chloride, alfacalcidol, ergocalciferol, levocarnil, and cysteamine ophthalmic drops.

The patient was started on RP103 on January 20, 2012. The patient was hospitalized from [REDACTED] (b) (6) for planned surgery to place bilateral transtympanic ventilation tubes. Her hospital course was uncomplicated.

The investigator assessed the reported event as not related to treatment with RP103. The applicant concurred with this assessment.

Comment: This reviewer agrees that the event does not appear to be treatment-related.

7.3.3 Dropouts and/or Discontinuations

One patient in RP103-02 discontinued for personal reasons. Two volunteers in RP103-05 discontinued due to adverse events (blurred vision and hematuria), and one volunteer withdrew consent. One volunteer withdrew from RP103-06 (reason unspecified). No patients discontinued from RP103-01. One patient discontinued from RP103-03 due to AE (planned knee surgery); her sibling was discontinued from the study at the same time. At the time of the 120-day Safety Update, four patients had

been discontinued to date from RP103-04, including two patients due to AE, one patient due to the physician’s decision, and one patient for “other” (unspecified) reasons.

Table 35: Summary of Patients Discontinuing from RP103 Trials

Reason for Discontinuation	RP103-01 N=9	RP103-02 N=18	RP103-03 N=43	RP103-04 N=60	RP103-05 N=20	RP103-06 N=20	All Patients N= 72
AE	0	0	1 (2%)	2 (3%)	2 (10%)	0	5 (7%)
Physician’s Decision	0	0	0	1 (2%)	0	0	0
Withdrew consent	0	0	0	0	1 (5%)	0	1 (1%)
Other	0	1 (6%)	1 (2%)	1 (2%)	0	1 (5%)	4 (6%)
Total	0	1 (6%)	2 (5%)	4 (7%)	3 (15%)	1 (5%)	10 (14%)

7.3.4 Significant Adverse Events

Three significant adverse events were reported in three individuals enrolled in RP103 trials, including hypokalemia, anaphylaxis, and allergic reaction. The narratives for the three significant adverse events are provided below:

Hypokalemia

One patient in RP103-01 (Patient 00008) experienced a severe (Grade 4) event of hypokalemia. The patient is an 8 year-old male with a history of hypokalemia. Concomitant medications included potassium supplementation (potassium chloride and spironolactone). The patient was noted to have a low potassium level (2.6 nmol/L; reference range 3.5 to 5.1 nmol/L) after dosing with 350 mg Cystagon on Day 3 of the trial (end-of-study visit). The patient had documented hypokalemia during screening (potassium 3.3) and his potassium levels continued to decrease on Days 1 and 2 of the trial (potassium levels 3.1 nmol/L and 3 nmol/L, respectively). The patient was administered extra doses of potassium during the visit; his potassium level at the time of discharge from the study visit was 2.6 nmol/L. The patient was asymptomatic throughout the event. During a telephone follow-up 3 days later, the patient’s father reported that the patient’s potassium level was 4.1 nmol/L. This event was assessed as not relate to treatment with study drug.

Anaphylaxis

In RP103-02, subject 120 experienced sudden epigastric pain, nausea and chills with an onset of about 3 hours after dosing with RP103. About 9 hours after dosing, he experienced vomiting and decreased voiding and was noted to have low-grade fever and significant orthostatic hypotension. He was transported to the emergency department and treated with intravenous fluids and Zofran with normalization of vital signs after 3 hours of rehydration. A work-up for sepsis was negative. The investigator assessed the event as probable anaphylaxis without respiratory or skin manifestations.

Allergic reaction

In RP103-05, Subject 101 experienced an allergic reaction characterized by blurred vision and other unspecified symptoms. He was treated with diphenhydramine and subsequently withdrawn from the trial. His follow-up eye exam was normal during a follow-up visit with an ophthalmologist.

Severe AEs

Four severe AEs were reported for 2 individuals enrolled in the bioequivalence trials (stomach ache, headache, shakiness in one patient and nausea in another individual); all four AEs were assessed as treatment-related. In RP103-01, in addition to the AE of severe hypokalemia described above, severe treatment-related AEs were reported in two patients (stomach ache and nausea); both events were assessed as treatment-related. In RP03-03, two severe AEs were reported in 2 patients, including a treatment-related event of abdominal pain/discomfort and an unrelated event of femur fracture. Four patients in RP103-04 have experienced severe AEs to date; no specific information was provided on the nature of these AEs.

Reviewer Comments:

This reviewer agrees with the assessments of treatment relationship for the aforementioned significant adverse events and severe AEs. The AEs assessed as treatment-related are known adverse drug reactions associated with treatment with cysteamine bitartrate and are described in Cystagon labeling.

7.3.5 Submission Specific Primary Safety Concerns

The labeling for Cystagon includes warnings and precautions for severe skin rashes, CNS symptoms and neurological complications (seizures, lethargy, somnolence, depression, encephalopathy, and pseudotumor cerebri), gastrointestinal bleeding or ulcers, and neutropenia. Skin rashes associated with cysteamine bitartrate treatment include skin lesions that resemble skin findings in patients with Ehler-Danlos syndrome.²⁰ Three individuals (one healthy volunteer and 2 patients) reported events of somnolence and three patients with nephropathic cystinosis reported events of lethargy in RP103 trials. All of these AEs were of mild severity. There were no reported events of severe skin rashes, gastrointestinal bleeding or ulcers, or neutropenia.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, the frequency of AEs was similar across trials with abdominal pain, nausea, headache, and dizziness being the most commonly reported events (reported in $\geq 5\%$ of individuals) in all RP103 trials (see [Table 36](#) and [Table 37](#)). In trials in healthy

²⁰ Besouw MTP, Bowker R, Cysteamine toxicity in patients with cystinosis, *J Pediatr* 2011; 159(6): 1004-1011.

volunteers, the most commonly reported AEs were diarrhea and nausea (24% each), abdominal pain /discomfort (22%) headache (12%), vomiting and abnormal urine odor (7% each), allergic reaction, dizziness, cold sweat, and pallor (5 % each).

Table 36: Most Commonly Reported Adverse Events in Healthy Volunteers (≥5%)

System Organ Class	Preferred Term	RP103-02 N=18	RP103-05 N=20	RP103-06 N=20	Total N=58
Gastrointestinal disorders					
	Abdominal pain/discomfort	2 (11%)	8 (40%)	3 (15%)	13 (22%)
	Diarrhea	2 (11%)	8 (40%)	4 (20%)	14 (24%)
	Eructation	0	1 (5%)	0	1 (2%)
	Flatulence	0	1 (5%)	0	1 (2%)
	Nausea	0	10 (50%)	4 (20%)	14 (24%)
	Vomiting	0	4 (20%)	0	4 (7%)
	Breath odor	0	0	1 (5%)	1 (2%)
Immune system disorders					
	Anaphylaxis/allergic rxn	1 (6%)	1 (5%)	1 (5%)	3 (5%)
Infections and infestations					
	Gastroenteritis	1 (6%)	0	0	1 (2%)
Musculoskeletal and connective tissue disorders					
	Jaw pain	1 (6%)	1 (5%)	0	2 (3%)
	Back pain	2 (11%)	0	0	2 (3%)
	Neck pain	1 (6%)	1 (5%)	0	2 (3%)
Nervous system disorders					
	Headache	2 (11%)	4 (20%)	1 (5%)	7 (12%)
	Somnolence	1 (6%)	0	0	1 (2%)
	Dizziness	1 (6%)	1 (5%)	1 (5%)	3 (5%)
Renal and urinary disorders					
	Hematuria	0	1 (5%)	0	1 (2%)
	Increased urination	0	1 (5%)	0	1 (2%)
	Abnormal urine odor	0	4 (20%)	0	4 (7%)
Skin and subcutaneous tissue disorders					
	Cold sweat	0	1 (5%)	2 (10%)	3 (5%)
Vascular disorders					
	Pallor	0	3 (15%)	2 (10%)	3 (5%)
Psychiatric disorders					
	Nervousness	0	2 (10%)	0	2 (3%)
Eye disorders					
	Blurred vision	0	0	1 (5%)	1 (2%)

In trials in patients with nephropathic cystinosis, AEs reported in ≥10% of patients included vomiting (19% to 40%), abdominal pain/discomfort (14% to 20%), headaches (9% to 20%), colds/URI/nasopharyngitis (0 to 17%), nausea (10% to 16%), ear infection/otitis media (0 to 13%), flu/influenza (0 to 13%), and diarrhea (2% to 10%). Adverse events reported in ≥5% of patients included anorexia/decreased appetite,

leg/extremity pain (0 to 8% each), breath odor, hypokalemia, cough, declining renal function/renal insufficiency, LVH/ventricular hypertrophy (0 to 7% each), fatigue, dizziness, genu valgum, skin odor, rash, and conjunctivitis (0 to 5% each).

Table 37: Most Commonly Reported Adverse Events in Patients with Nephropathic Cystinosis (≥5%)

System Organ Class	Preferred Term	RP103-01 N=9		RP103-03 N=43		RP103-04 N=60
		C N=9	R N=9	C N=41	R N=43	R N=60
General disorders and administration site conditions						
	Anorexia/decreased appetite	1 (11%)	0	2 (5%)	1 (2%)	5 (8%)
	Fatigue	0	0	0	1 (2%)	3 (5%)
	Thirstiness	4 (44%)	2 (22%)	0	0	0
Gastrointestinal disorders						
	Abdominal pain/discomfort	1 (11%)	0	0	6 (14%)	12 (20%)
	Diarrhea	1 (11%)	0	1 (2%)	1 (2%)	6 (10%)
	Nausea	3 (33%)	0	3 (7%)	7 (16%)	6 (10%)
	Vomiting/emesis	4 (44%)	0	5 (12%)	8 (19%)	24 (40%)
	Breath odor	1 (11%)	0	0	0	4 (7%)
Nervous system disorders						
	Dizziness	0	0	0	2 (5%)	2 (3%)
	Headache	0	0	0	4 (9%)	12 (20%)
Infections and infestations						
	Cold/URI/nasopharyngitis	0	0	1 (2%)	1 (2%)	10 (17%)
	Ear infection/otitis media	0	0	0	0	7 (12%)
	Flu/flu symptoms	0	0	0	0	8 (13%)
	Gastroenteritis/GI virus/stomach flu	0	0	0	1 (2%)	6 (10%)
	Hypokalemia	1 (11%)	0	0	3 (7%)	1 (2%)

C= Cystagon R=RP103

TABLE 37: Most Commonly Reported Adverse Events in Nephropathic Cystinosis Patients (cont'd)

System Organ Class	Preferred Term	RP103-01 N=9		RP103-03 N=43		RP103-04 N=60
		C N=9	R N=9	C N=41	R N=43	R N=60
Musculoskeletal and connective tissue disorders						
	Genu valgum	0	0	0	1 (2%)	3 (5%)
	Leg pain/extremity pain	0	0	0	1 (2%)	5 (8%)
	Muscle spasms	0	0	0	0	3 (5%)
Renal and urinary disorders						
	Declining renal function/renal insufficiency	0	0	1 (2%)	3 (7%)	0
Respiratory, thoracic and mediastinal disorders						
	Cough	0	0	0	2 (5%)	4 (7%)
	Epistaxis/nose bleed	0	0	0	0	2 (3%)
	Rhinorrhea	0	0	0	0	2(3%)
Skin and subcutaneous tissue disorders						
	Abnormal skin odor	1 (11%)	0	0	0	3(5%)
	Rash	0	0	1 (2%)	1 (2%)	3 (5%)
Cardiac Disorders						
	AV block	0	0	2 (5%)	0	1 (2%)
	LVH/Ventricular hypertrophy	0	0	1 (2%)	1 (2%)	4(7%)
Eye disorders						
	Conjunctivitis	0	0	0	1 (2%)	3 (5%)

C= Cystagon R=RP103

In RP103-03, there was an almost 2-fold difference between the incidence of AEs during the RP103 treatment period (58%) and the incidence of AEs during the Cystagon treatment period (32%). There was a similar differential in the incidences of AEs assessed as treatment-related during the RP103 treatment period and the Cystagon treatment period (26% incidence and 15% incidence, respectively). The applicant postulated that the observed differential may have been due to the restriction on use of PPIs during the RP103 treatment period, noting that gastrointestinal manifestations of cystinosis overlap with known gastrointestinal adverse effect of cysteamine bitartrate.

Reviewer Comments:

Overall, the safety profile of RP103 is consistent with the safety profile for Cystagon. Study RP103-03 was the only trial that directly compared RP103 to Cystagon. The higher overall incidence of AEs observed during RP103 treatment in this trial appears to be due primarily to the higher incidence of gastrointestinal AEs with treatment with RP103. This reviewer agrees that the restriction of use of PPIs during RP103 treatment likely contributed to the observed differential.

7.4.2 Laboratory Findings

Five patients experienced AEs of hypokalemia (one RP103-01 patient, three RP103-03 patients [including one RP103-03 patient who experienced a SAE of hypokalemia], and one RP103-04 patient). All hypokalemia events occurred while patients were taking RP103. All of these patients were receiving potassium supplements for treatment of nephropathic cystinosis. Two AEs were reported for two RP103-03 patients while receiving Cystagon (hypertriglyceridemia and low hemoglobin). None of the laboratory AEs were considered to be related to treatment with RP103. A review of descriptive statistics for laboratory data did not reveal any clinical relevant changes compared to baseline.

7.4.3 Vital Signs

Two AEs of hypertension were reported in two RP103-03 patients, including an event that occurred in one patient who was noncompliant with hypertension medications during treatment with Cystagon. One RP103-03 patient experienced an event of hypotension. None of the vital signs AEs were considered to be related to treatment with RP103. A review of descriptive statistics for vital sign data did not reveal any clinical relevant changes compared to baseline.

7.4.4 Electrocardiograms (ECGs)

There were six AEs of ECG abnormalities in six RP103-03 patients, including Grade 1 atrioventricular block (2 patients), left ventricular hypertrophy (2 patients), prolonged QT segment (1 patient), tachycardia (1 patient), and right ventricular hypertrophy and left ventricular hypertrophy (1 patients). One RP103-04 patient experienced an event of prolonged QT segment. None of the ECG abnormality AEs were considered to be related to treatment with RP103.

Findings from an earlier review of safety data (safety data cut-off date of December 31, 2011) had suggested that there were clinically significant changes in heart rate (decreased heart rate) and PR interval (increased PR interval) over time. However, a review of longer term data (safety data cut-off date of June 22, 2012) indicated that there were minimal changes in these parameters over time (mean heart rate decrease

of 7 beats per minute [n=38] and mean PR interval increase of 4.2 ± 16 msec [n=37] at Month 6).

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this clinical development program.

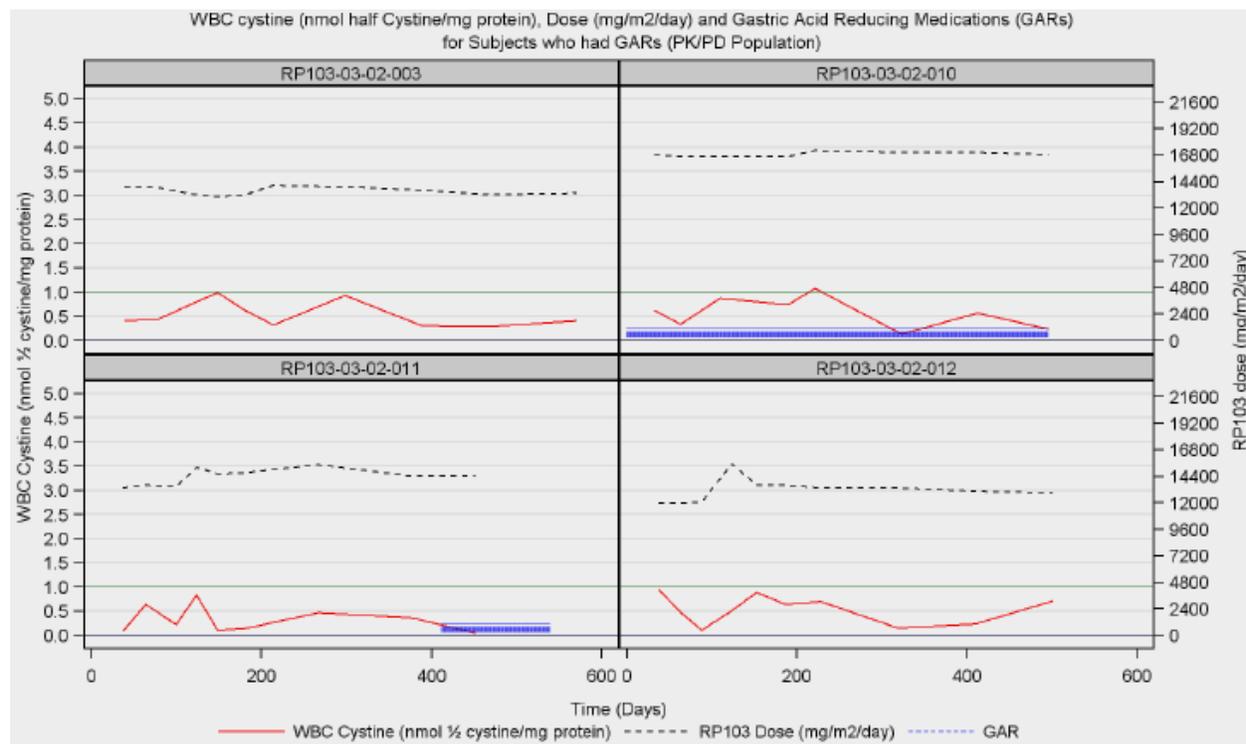
7.5 Other Safety Explorations

The applicant assessed the long-term safety of RP103 in relation to concomitant use of GAR medications and renal function.

Concomitant use of GAR medications

The applicant analyzed the safety database for RP103-04 to assess the impact of concomitant use of GARs with RP103. The safety concern was the potential for these agents to interfere with RP103 absorption by increasing gastric pH. Although patients were requested to suspend the use of GAR medications during RP103 trials, some patients continued to take GAR medications intermittently or continuously. Twenty of 60 patients (33%) used GAR medications for some period of time during the trial. An analysis of the PD and RP103 dosing data for these patients did not reveal any significant changes in WBC cystine levels or increases in RP103 dosing with concomitant GAR medication use. [Figure 10](#) is a representative sample of the results of this safety analysis.

Figure 10: WBC Cystine (nmol ½ cystine/mg protein), Dose (mg/m2/day) & Gastric Acid Reduction Medications (GARs) for Patients who had GARs (RP103-04 PK/PD Population)

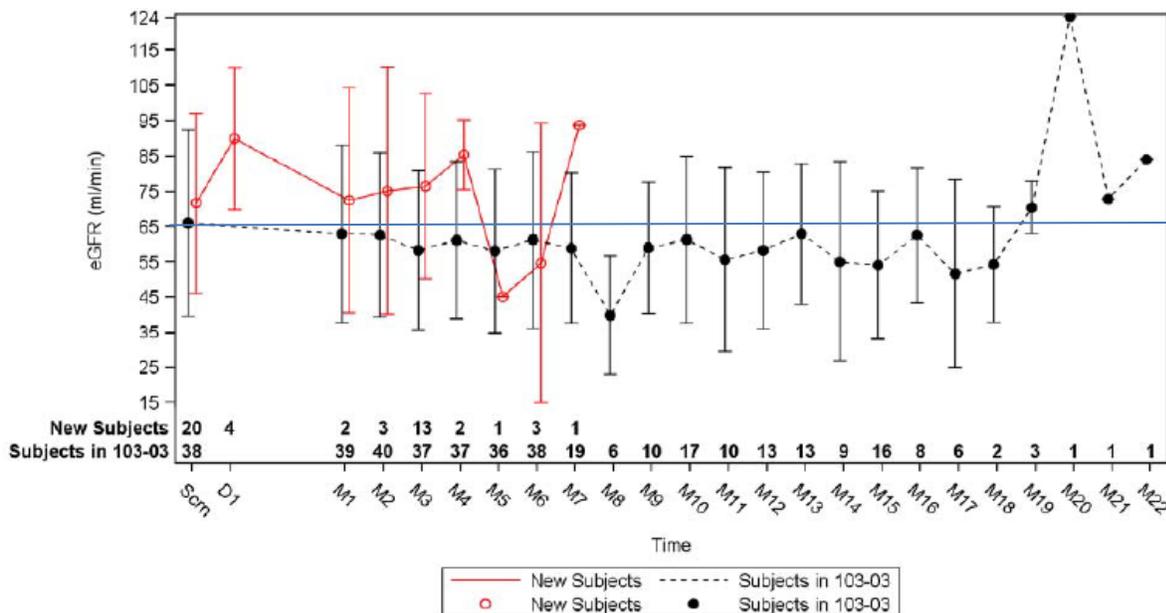


Source: NDA 203389 120-day Safety Update- Tables, Listings, and Figures

Renal Function

The applicant evaluated renal function (as measured by eGFR) during treatment with RP103 up to 22 months. The applicant stated that mean eGFR appeared to be stable over time (see [Figure 11](#)).

Figure 11: Evolution of eGFR (mL/min) Over Time (RP103-04 Safety Population)



Scrn=Screening; D=Day; M=Month
 Source: NDA 203389 120-Day Safety Update dated January 30, 2013

Reviewer Comment:

This reviewer agrees that there did not appear to be any short-term changes in renal function (i.e., changes over a 12 month treatment period). However, given the wide variability in patient eGFR values and the small sample sizes for eGFR assessments beyond Month 12 of treatment, there are not sufficient data to evaluate the longer term impact of RP103 on renal function.

7.5.1 Dose Dependency for Adverse Events

[Table 38](#) summarizes adverse events by RP103 dose (<1.95 g/m²/day and ≥1.95 g/m²/day). In RP103-03, 8/43 patients received RP103 doses ≥1.95 g/m²/day. Of these patients, 7/8 (88%) patients experienced 16 AEs during the RP103 treatment period. Twenty-eight of 35 patients who received RP103 doses <1.95g/m²/day experienced 60 AEs during the RP103 treatment period. The most common AEs reported for patients receiving high doses of RP103 were nausea, vomiting, and anorexia (4 patients each). The most common AEs reported for patients receiving doses ≥1.95 g/m²/day were nausea and vomiting (2 patients each; 25%). The most common AEs reported for patients receiving doses ≤1.95 g/m²/day were vomiting (6 patients; 17%), nausea and abdominal pain/discomfort (5 patients each; 14%), headache and hypokalemia (3 patients each; 9%), and dizziness and renal insufficiency/decreased renal function (2

patients each; 6%). Only three patients in RP103 received doses ≥ 1.95 g/m²/day at any point during the course of the study. None of these patients received doses ≥ 1.95 g/m²/day continuously during the study. Therefore, there are insufficient data to evaluate the relationship of dose to long-term safety.

Reviewer Comments:

No clear dose relationship to adverse events was observed during short-term treatment with RP103. This appears contradictory to the higher incidence of adverse events at doses ≥ 1.95 g/m²/day observed in clinical trials for Cystagon. However, since RP103 dosing was based on each individual patient's prior dose of Cystagon, the patients receiving high doses of RP103 were patients who had tolerated equal or higher doses of Cystagon. Thus, these were patients who had already demonstrated tolerance of higher doses.

Table 38: RP103-03 Most Commonly Reported AEs ($\geq 5\%$) by Total Daily RP103 Dose

MedDRA SOC/Preferred Term	Total daily RP103 dose		Total patients N=43
	≥ 1.95 g/m ² /day mg N=8	< 1.95 g/m ² /day mg N=35	
# of patients with AEs	7 (88%)	28 (80%)	35 (81%)
Gastrointestinal disorders			
Abdominal pain/Discomfort	1 (13%)	5 (14%)	6 (14%)
Vomiting	2 (25%)	6 (17%)	8 (19%)
Nausea	2 (25%)	5 (14%)	7 (16%)
Nervous system disorders			
Headaches	1 (13%)	3 (9%)	4 (10%)
Dizziness	0	2 (6%)	2 (5%)
Metabolism and nutrition disorders			
Hypokalemia	0	3 (9%)	3 (7%)
Renal & urinary disorders			
Renal insufficiency/decreased renal function	0	2 (6%)	2 (5%)

7.5.2 Time Dependency for Adverse Events

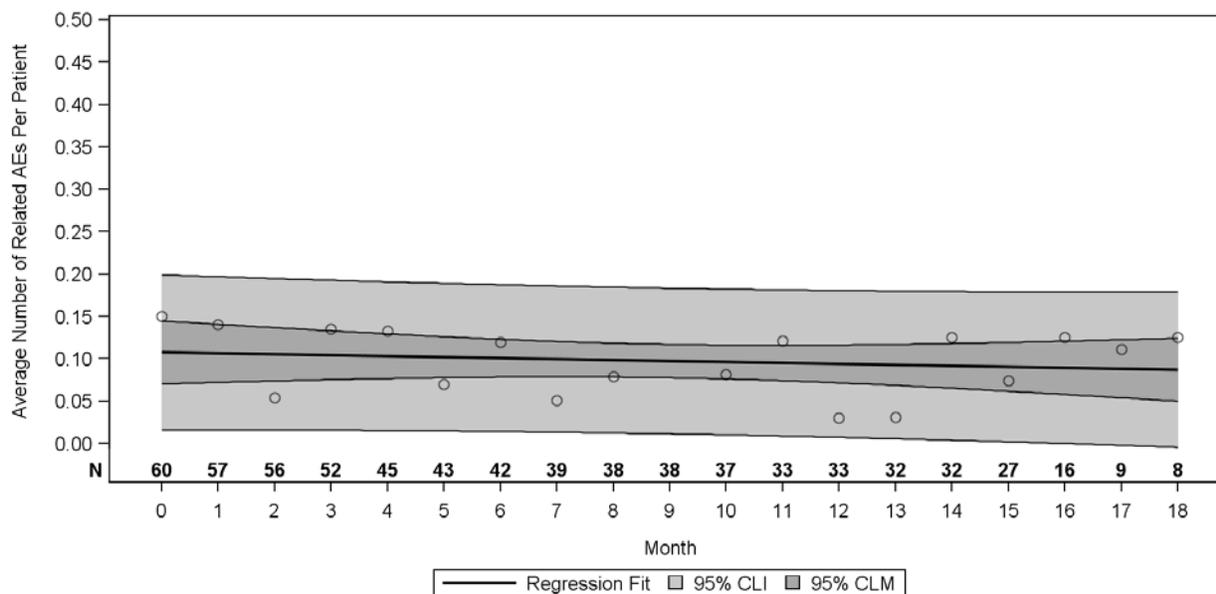
The applicant performed a regression analysis in the safety population for RP103-04 of the incidence of gastrointestinal treatment-emergent adverse events (TEAEs) assessed as treatment-related, including abdominal pain, breath odor, nausea, vomiting, and diarrhea. To date, gastrointestinal TEAEs have been reported in 36/60 (60%) patients enrolled in RP103-04. Twenty-five of 60 RP103-04 patients (42%) were assessed as having treatment-related gastrointestinal TEAEs (see [Table 39](#)). Other treatment-related AEs reported for RP103-04 patients included abnormal skin odor (4 patients; 7%), decreased appetite (3 patients; 5%), and fatigue (2 patients; 3%). The applicant's

analysis indicated that the incidence of treatment-related gastrointestinal AEs as well as the overall incidence of treatment-related AEs reported per month decreased slightly over time (see [Figure 12](#) and [Figure 13](#)).

Table 39: RP103-04 Gastrointestinal TEAEs for RP103-04 by Relationship To Treatment

MedDRA SOC/Preferred term	ALL TEAEs N=60	Treatment-Related TEAEs N=60
# of unique patients		
Gastrointestinal disorder		
Vomiting	24	17
Abdominal pain/discomfort	12	8
Nausea	6	5
Diarrhea	6	3
Breath odor	4	4
# of unique patients with any gastrointestinal TEAE	36	25

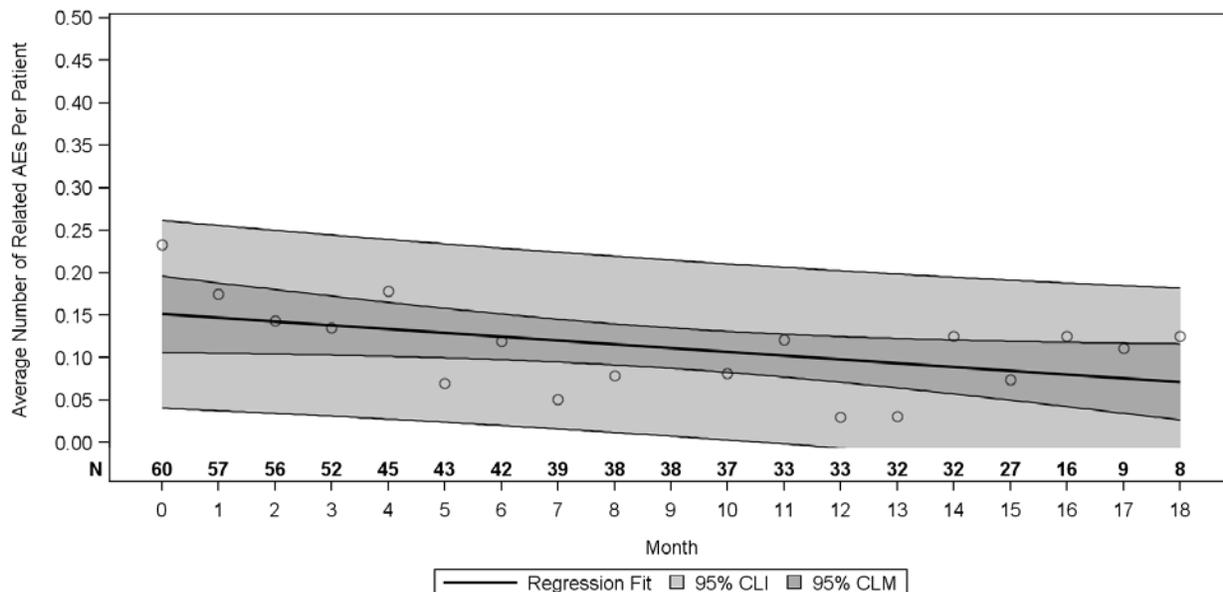
Figure 12: Evolution of Incidence of Gastrointestinal Related Adverse Events by Month on Treatment (RP103-04 Safety Population)



Note: Treatment-emergent adverse events (TEAE) with relationship as possibly, probably and definitely related are included.
 TEAE is an AE that started on or after the first dose of study drug (RP103) in study RP103-04.
 Month is derived based on AE start date and 1st dose date in study RP103-04. Partial AE start date is imputed by using earliest possible date on or after 1st dose date of RP103-04.

Source: NDA 203389 120-Day Safety Update- Tables, Listings and Figures, Figure 1

Figure 13: Evolution of Incidence of Related Adverse Events by Month on Treatment (RP103-04 Safety Population)



Note: Treatment-emergent adverse events (TEAE) with relationship as possibly, probably and definitely related are included. TEAE is an AE that started on or after the first dose of study drug (RP103) in study RP103-04. Month is derived based on AE start date and 1st dose date in study RP103-04. Partial AE start date is imputed by using earliest possible date on or after 1st dose date of RP103-04.

Source: NDA 203389 120-Day Safety Update- Tables, Listings and Figures, Figure 2

7.5.3 Drug-Demographic Interactions

No drug-demographic interactions were examined with regard to safety data.

7.5.4 Drug-Disease Interactions

No data are available for drug-disease interactions.

7.5.5 Drug-Drug Interactions

No drug-drug interactions have been described for Cystagon and none were identified in clinical trials for RP103. The labeling for Cystagon states: “Cystagon can be administered with electrolyte and mineral replacements necessary for the management of the Fanconi Syndrome as well as vitamin D and thyroid hormone. Based on transporter study results indicating that RP103 was a substrate for OCT2, the applicant proposes (b) (4)

(b) (4)

[Section 4.4.4](#) and [Section 7.2.5](#) of this review also address the issue of potential drug-drug interactions.

7.6 Additional Safety Evaluations

No additional safety evaluations were performed for RP103.

7.6.1 Human Carcinogenicity

There was no evidence of human carcinogenicity in the safety evaluation.

7.6.2 Human Reproduction and Pregnancy Data

No pregnant women participated in clinical trials for RP103. The reference product Cystagon has a pregnancy category C classification. As noted earlier, the labeling for Cystagon notes that teratogenic findings were observed in preclinical studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

A total of 45 pediatric patients ages 6 years to 17 years were enrolled in RP103-01 and RP103-03. The applicant reports that 58 pediatric patients ages 21 years or younger have been enrolled in the ongoing RP103-04 trial, including 40 patients who had completed RP103-03. The youngest patient enrolled in RP103 trials to date is 2 years old. Although height and weight data were collected in the trials, no formal assessments of growth were included in any of the trials. The applicant has submitted a Proposed Pediatric Study Request for Agency review.

Reviewer Comments:

At the time of this submission, the majority of patients had been treated with RP103 for less than one year. Given the short treatment duration and the lack of formal growth assessments in the trial, there is limited ability to assess the impact of RP103 on pediatric growth. These assessments should be included in the protocol for the applicant's proposed pediatric trial.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reported cases of overdose for this clinical development program. This product has a low potential for drug abuse due to its objectionable taste and a known side effect of halitosis and body odor. This drug is not associated with withdrawal or rebound effects.

7.7 Additional Submissions / Safety Issues

Multiple clinical information requests were sent to the applicant, including requests for additional PK/PD and safety data related to body surface area-based dosing (see [Table 2](#) for a listing of Agency information requests). These data were reviewed during this review cycle.

The applicant submitted a proposed pharmacovigilance plan for RP103 (see [Table 40](#)). The plan includes the following risk minimization activities:

Table 40: Summary of Proposed Pharmacovigilance Activities for RP103

(b) (4)

Reviewer's Comment:

The safety profile of this product appears to be similar to the safety profile of Cystagon. Based on the post-marketing experience with Cystagon, it is this reviewer's opinion that routine pharmacovigilance activities are adequate to minimize risk with RP103.

8 Postmarket Experience

There is no postmarket experience with this product.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

This is labeling for a 505(b)2 drug product. The labeling will be in PLR format. Content and formatting were reviewed to meet the latest best-practices. Labeling for Cystagon was reviewed to ensure consistency across cysteamine products. The final labeling contains all of the labeling revisions negotiated with the applicant.

I recommend that RP103 be indicated for management of nephropathic cystinosis in pediatric patients 6 years and older and in adult patients, including treatment-naïve patients and patients switching from Cystagon. Dosing should be based on body surface area for all patients without regard to age or weight.

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

/s/

CARLA L EPPS
04/26/2013
NDA 203-389 Clinical Review
Action Recommendation: Approval

LARA DIMICK-SANTOS
04/26/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Agency agreed to endpoint but not to overall SPA submitted by sponsor
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	rare disease- ICH guidelines not applicable
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			waiver (orphan product) sponsor is proposing pediatric study in children (b) (4)
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			Response to IR received 5/29/12- rationale adequate
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			GCP statement in each individual study; no general statement for overall NDA

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Please provide a rationale for inclusion of data from non-US study sites (Sites 5, 6, 7, 8, and 9) for Studies RP103-03 and RP-103-04.

Carla Epps, MD
Reviewing Medical Officer

May 29, 2012
Date

Clinical Team Leader

Date

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

/s/

CARLA L EPPS
06/01/2012

LYNNE P YAO
06/01/2012