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RESEARCH**

APPLICATION NUMBER:

203389Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL REVIEW

Application Type	NDA
Application Number(s)	203-389
Priority or Standard	Standard
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Division / Office	DGIEP
Reviewer Name(s)	Lara Dimick-Santos, MD, FACS
Review Completion Date	4/30/2013
Established Name	cysteamine bitartrate (RP103)
(Proposed) Trade Name	PROCYSBI®
Therapeutic Class	Cystine depleting agent
Applicant	Raptor Therapeutics
Formulation(s)	Delayed-release capsules, 25 mg and 75 mg
Dosing Regimen	Two times daily Maintenance dose: Age ≥ 6 years: 1.3 gram/m ² /day
Indication(s)	Nephropathic cystinosis
Intended Population(s)	Children ≥ 6 years and adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

PROCYSBI (RP103) is recommended for approval. This drug is an extended release, enteric-coated microbead formulation of the already approved reference drug Cystagon®, an immediate release formulation of cysteamine bitartrate. Cystagon must be taken every 6 hours around the clock, making compliance difficult. PROCYSBI is to be taken every 12 hours. This recommendation is made on the basis of a single pivotal clinical trial showing non-inferiority of PROCYSBI to Cystagon. The clinical trial was conducted only in children 6 years of age or older and adults, therefore the drug is recommended only for this population at this time. There is an ongoing open label extension trial which will assess the benefit of PROCYSBI in children less than 6 years of age, and in patients who have received a kidney transplant, however only interim results are available with final results pending. The sponsor plans to submit the (b) (4) data for children less than 6 years of age in the last quarter of 2013.

The pivotal clinical trial (RP103-03) for approval of PROCYSBI was conducted in previously treated patients who were switched from Cystagon to PROCYSBI in a randomized, crossover trial design; however because this is the same chemical entity as Cystagon we recommend that PROCYSBI be approved for both treatment naive and previously treated patients.

1.2 Risk Benefit Assessment

Nephropathic Cystinosis is an autosomal recessive disorder characterized by an accumulation of the amino acid cystine in lysosomes throughout the body. The disease presents in three clinical forms, infantile, juvenile and adult. The infantile form is the most frequent and severe form of the disease. The infantile and juvenile forms lead invariably to renal failure and without treatment to death, though the juvenile form can have a variable time course. There are multiple non-renal manifestations, such as encephalopathy, photophobia, muscle wasting, failure to thrive, and difficulty swallowing. The adult form is generally less severe and manifests as ocular changes only. This disease is obviously severe and life threatening in the infantile and juvenile on set subtypes.

The main stay of treatment for the patients with systemic Cystinosis is administration of cysteamine which can postpone or even prevent the deterioration in renal function and the development of extra-renal complications, and improve growth. It should be administered as soon as the diagnosis is made and continued for life. Cystagon® (cysteamine bitartrate, the reference product) was approved for this indication in 1994, however as mentioned above it must be given every six hours around the clock,

requiring waking patients during sleeping hours. PROCYSBI (the current application) is a delayed release form of cysteamine bitartrate and can be administered every twelve hours, improving life style and hopefully compliance for these patients. The main side effects of treatment are gastrointestinal discomfort (hypothesized to be due to the release of gastrin and the resulting stimulation of acid secretion in the stomach), bad breath and sweat odor (secondary to metabolites of cysteamine). Allergic reactions, fever, seizures, and neutropenia are also reported, especially when the dose of the drug is abruptly increased. Most patients taking Cystagon have required concomitant use of gastric acid reducing (GAR) medications to control symptoms.

The efficacy of RP103 was principally demonstrated in a single pivotal trial (RP103-03). RP103-03 was a 9-week, open-label, multicenter, randomized, cross-over, pharmacokinetic (PK) and pharmacodynamics (PD), non-inferiority (margin - 0.3 nmol ½ cystine/mg protein) trial designed to evaluate the safety and efficacy of RP103 (cysteamine bitartrate delayed release capsules) compared to Cystagon. Forty-three patients were randomized to one of the two treatment sequences, 41 patients completed the trial. In this trial, RP103 was determined to be non-inferior to Cystagon with regard to steady-state trough WBC cystine levels. There were no statistical issues that impacted the overall conclusions of trial RP103-03. The study's design was adjudicated as being adequate, and the applicant's corresponding analysis plan was deemed appropriate. The only potential statistical issue pertains to the study's non-inferiority margin which was ultimately deemed acceptable by the review team. See the discussion in the Efficacy Summary on page 41. Consequently, results from trial RP103-03 are viewed positively as the formal basis for the products' efficacy claim.

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.

The apparent sustained efficacy profile during the extension study RP103-04 further supports the efficacy claim for PROCYSBI (RP103). There was no secondary efficacy endpoints pre-specified by the applicant hence no corresponding secondary efficacy endpoint analyses existed.

Benefit is demonstrated for this product in that it meets the primary non-inferiority claim as compared to the reference product, and that it may be administered every 12 hours as opposed to the every 6 hour regiment required by the reference product. This decreased frequency of dosing should be more convenient for patients and is postulated, but not proven, to increase compliance. In addition, the enteric-coated microbeads of RP103 can be sprinkled directly onto food making it easier to dose infants and children too young to take intact capsules. As cystinosis is usually diagnosed by age one, adequate treatment during these early years would be critical to prevent organ deterioration. However, efficacy and safety have not yet been proven in

children less than 6 years of age and therefore the product is not yet recommended for these younger patients.

The overall safety profile of RP103 appears to be similar to the reference product Cystagon, although a higher incidence of gastrointestinal adverse events were observed in trial RP103-03 when comparing RP103 with Cystagon (which is discussed in more detail below). Evidence of long-term safety is based on 27 adult and pediatric patients who were treated for at least 15 months. During the entire RP103 development program, there were a cumulative total of zero deaths and two treatment-related serious adverse events (abdominal discomfort and constipation). The most common non-serious adverse events (i.e. > 5% of patients) were vomiting, nausea, abdominal pain, dizziness, and headaches.

The sponsor postulated that the delayed release formulation would result in less gastrin release and a decrease in dyspepsia symptoms and requirements for GAR medications. However, this was not demonstrated in the controlled trial. The sponsor elected to discontinue all GAR medications prior to the patients starting the Procysbi phase of the trial. Subsequently there was an increase incidence of gastrointestinal AE's in the Procysbi arm as compared to the placebo arm, in which the patients continued their previous GAR medication.

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.

There were not any consistent patterns in change from baseline in quality of life or swallowing function in either treatment group.

The benefit versus risk evaluation for PROCYSBI (RP103) for treatment of nephropathic cystinosis favors the approval of this application. Procysbi is an extended release formulation of the reference drug Cystagon and demonstrates non-inferiority in the pivotal trial. The risk profile appears to be very similar to the reference drug which is expected as they are the same chemical entities. The extended release formulation allows dosing every 12 hours instead of every 6 hours making dosing more convenient for patients.

The applicant submitted a Proposed Pediatric Study Request to evaluate (b) (4), (b) (4) PROCYSBI in pediatric patients (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. In addition, the applicant submitted a proposed pharmacovigilance plan that includes controlled distribution. While still under review at the time of this document, the overall pharmacovigilance plan appears adequate to evaluate for and mitigate post-market risk.

1. To complete drug product specification testing for elemental impurities.

Final Report Submission: June 5, 2011

2 Introduction and Regulatory Background

See Section 2.6 Other Relevant Background Information for discussion of nephropathic cystinosis, and current therapy.

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. It will be manufactured in 25 mg and 75 mg capsules for marketing.

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)

Reviewer Comment:

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)

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

2.2 Currently Available Treatments for Proposed Indications

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

During a 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 was an appropriate primary efficiency endpoint for the pivotal study. The Applicant submitted a SPA for RP103-03 in March of 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. The Applicant submitted a second SPA in May of 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 the pivotal trial. The Applicant submitted NDA 203389 application on March 30, 2012. In December 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.

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.

2.6 Other Relevant Background Information

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*, which encodes the lysosomal cystine carrier cystinosin.

Depending on the age at presentation and the degree of disease severity, three clinical forms of cystinosis are distinguished. 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. As the target tissue cystine levels necessary to prevent the progression of renal disease and the occurrence of extra-renal complications are still unknown, the 0.9 percentile of heterozygote values in the PMN cells is mostly recommended as an upper cystine limit before the next dose of cysteamine is given (<0.5 nmol cystine per mg protein). Historically, cystine depletion therapy targeted achievement of WBC cystine levels below 1 nmol $\frac{1}{2}$ 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 $\frac{1}{2}$ cystine/mg protein).⁵ See Section 6.2 Additional Efficacy Issues/Analyses for discussion of measuring cystine levels.

The main side effects of treatment are gastrointestinal discomfort (due to the release of gastrin and the resulting stimulation of H⁺ secretion in the stomach), and bad breath and sweat odor (secondary to metabolites of cysteamine). Allergic reactions, fever, seizures, and neutropenia are also reported, especially when the dose of the drug is abruptly increased. Most patients taking Cystagon have required concomitant use of gastric acid reducing (GAR) medications to control symptoms. Recently, (b) (4) patients treated with high cysteamine doses were reported to exhibit endothelial proliferative lesions on the elbows, skin striae, and bone and muscular pain, which improved or disappeared after lowering the cysteamine dosing (personal communication from Orphan Europe). Because of these adverse events, using cysteamine doses above the recommended 1.9 g/m² should be discouraged.

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.

Ophthalmic cysteamine drops were recently approved to treat corneal accumulation on cystine. Preclinical investigations include evaluation of bone marrow and hematopoietic stem cell transplantation in a mouse model of cystinosis.⁶

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

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. Despite the issues with the submission described above, the submission was well organized and of adequate quality to allow comprehensive review of the data.

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 Harmonization (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. These sites were selected for inspection because of their high enrollment and geographic location (one domestic and one foreign site). The DSI inspector 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) (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. See Section 6.2 Additional Efficacy Issues/Analyses for discussion of measurement of cystine levels.

3.3 Financial Disclosures

The Applicant stated that no investigators involved in the clinical trials submitted in support 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 aminothiols, 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).

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. See also Section 6.1 Data and Analysis Quality. 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 requirement with a fulfillment date of June 5, 2013, which is acceptable to the CMC reviewers. 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 concluded that the applicant had provided sufficient information to assure identity, strength, purity, and quality of the drug product. Issues regarding information on dosage forms and strengths, dosage and administration, and storage and handling of the drug product are being addressed with labeling (see Section 6.2 Additional Efficacy Issues/Analyses).

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. The results of this study are being addressed in labeling information on drug administration (see Section 9.2 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.

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.

The official Established Pharmacologic Class (EPC) is discussed in an addendum to the preclinical pharmacology review, while the official EPC should technically be (b) (4) a more accurate description of the pharmacological action of this drug would be “cystine depleting agent” and this is the final recommendation of the team for the EPC.

Pharmacology/Toxicology Labeling Recommendations

Changes to “Full Prescribing Information”

(b) (4)

Pharmacology/Toxicology Action Recommendation

Pharmacology/Toxicology recommends for 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 Phase 1 studies in healthy volunteers included three single-dose pharmacokinetic (PK) studies, of which one also included an exploration of the food effect. The sponsor has also submitted data from nine *in vitro* studies.

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 aminothioliol 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 ½ cystine/mg protein and usually <1 nmol ½ cystine/mg protein, respectively. WBC cystine level was the primary efficacy endpoint in the pivotal trial (RP103-03) and its extension study (RP103-04).

PK/PD in Cystinosis Patients

RP103 achieves maximum systemic exposure approximately 3 hours post-dose in cystinosis patients. The mean WBC cystine declines following administration RP103 and closely follows the pharmacokinetics of the drug. Relative to IR Cystagon, there is

a slower decline in WBC cystine and a slower return to baseline in WBC cystine compared to RP103 treated patients. The mean WBC cystine levels all remain below 1 nmol/ ½ cystine/mg protein during the 12 hour dosing interval. RP103 is titrated to WBC cystine response; therefore, the dose is highly individualized.

4.4.3 Pharmacokinetics

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 (StudyRP103-05) 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.

- 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:
 - Match the total daily dose of Cystagon that patients are on when switched to RP103 instead of reducing the amount of drug received to ensure better reduction of white-blood-cell cystine concentrations.
 - When increasing the dose, adjust the dose amount by 25%.

See recommendations for labeling revisions in Section 9.2 Labeling Recommendations.

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 Review of Safety.

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 1: Table of RP103 Studies & Clinical Trials.

Table 1: 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
Review of Safety

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 RP103-01 (Pilot study)

A. 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. 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.

B. 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 (GSRS) 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).

C. 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.

D. 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).

E. Review of RP103-01 Study Results

1. 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 2). 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 2: 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

Review of Efficacy RP103-01

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, PK data from Study RP103-04 corroborated these trial simulation results. See discussion in Section 6.2 Additional Efficacy Issues/Analyses.

a. PK Analysis

Following administration of a 450 mg normalized dose, mean C_{max} , AUC_{0-6h} and AUC_{0-12h} (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 $\mu\text{mol}^*\text{h/L}$; AUC_{0-12h} 118.2 ± 54.6 $\mu\text{mol}^*\text{h/L}$) compared to Cystagon (C_{max} 37.72 ± 12.10 $\mu\text{mol/L/mg}$; AUC_{0-6h} 105.9 ± 62.3 $\mu\text{mol}^*\text{h/L}$; AUC_{0-12h} 211.9 ± 124.6 $\mu\text{mol}^*\text{h/L}$). However, the mean normalized dose AUC_{∞} was higher for RP103 (146.7 ± 69.2 $\mu\text{mol}^*\text{h/L}$) compared to Cystagon (118 ± 66.6 $\mu\text{mol}^*\text{h/L}$). 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 3 summarizes mean PK values for Cystagon and RP103 following a 450 mg normalized dose.

Table 3: 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_{∞} ($\mu\text{mol}^*\text{h/L}$)	118 (66.6)	146.7 (69.2)
AUC_{0-6h} ($\mu\text{mol}^*\text{h/L}$)	105.9 (62.3)	89.6 (45.8)
AUC_{0-12h} ($\mu\text{mol}^*\text{h/L}$)	211.9 (124.6)	118.2 (54.6)

SD= standard deviation

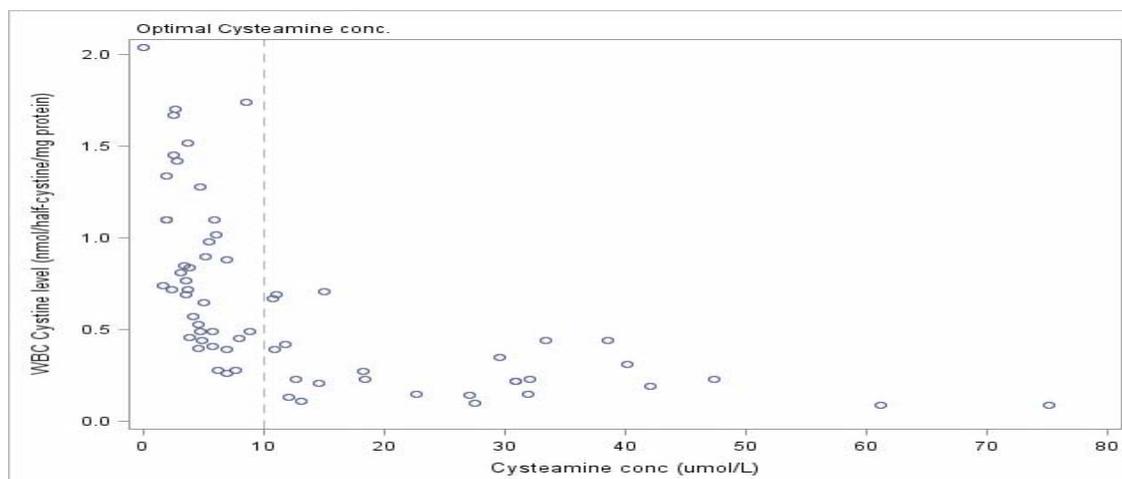
Source: Final Report: PK/PD and Safety Summary for Study RP103-01 (dated February 9, 2010), Table 4

b. 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 1).

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 $\text{nmol } \frac{1}{2}$ cystine/mg protein from an initial value of 2.015 $\text{nmol } \frac{1}{2}$ cystine/mg protein.

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



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

Based on a regression analysis of the dose-normalized AUC_{0-12h} 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).

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

See Section 4.4 Clinical Pharmacology for a discussion of clinical pharmacology data for these trials. Safety data for these trials are reviewed in Section 7 Review of Safety.

5.3.3 RP103-03 (Pivotal trial)

A. General Design and Objectives

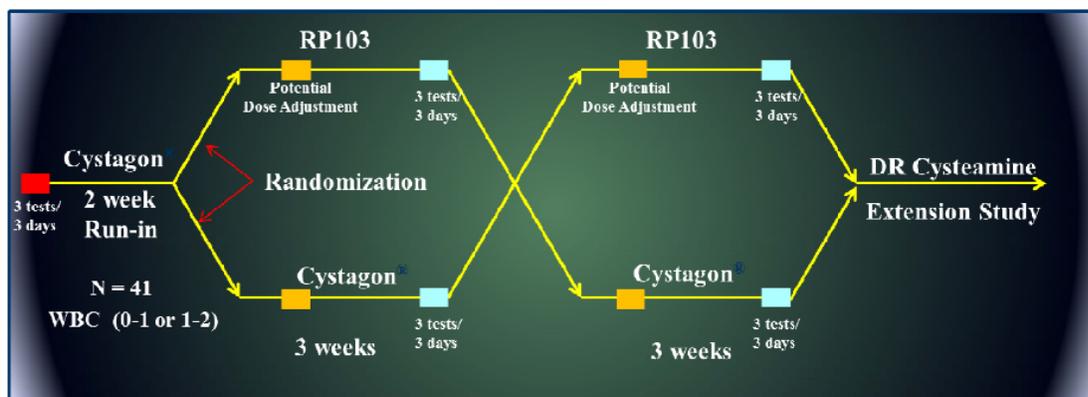
This was a 9-week, open-label, multicenter, randomized, cross-over, pharmacokinetic (PK) and pharmacodynamics (PD), non-inferiority trial, in patients 6 years of age or older. It was designed to evaluate the safety and efficacy of RP103 (cysteamine bitartrate delayed release capsules) compared to Cystagon in patients with nephropathic cystinosis. See Figure 2: Schematic of PR103-03 Trial Design

Nephropathic cystinosis patients 6 years of age or older, 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.

The study consisted of two treatment periods: Period 1 (Weeks 4 through 6; ± 3 days) and Period 2 (Weeks 7 through 9; ± 3 days). Prior to treatment, eligible patients underwent a 2 week Run-in Period (Weeks 2 through 3) of Cystagon administered every 6 hours. Available safety data and WBC cystine levels collected during this Run-in period were reviewed to confirm study eligibility. On Week 3, Day 7, patients (who had their eligibility confirmed) were randomized (in an open-labeled fashion and on a 1:1 ratio, in accordance with a computer-generated central randomization schedule) to one of two treatment sequences: Treatment Arm A – 3 weeks (Period 1 i.e. Weeks 4 through 6; ± 3 days) treatment with RP103 every 12 hours followed by crossover to 3 weeks (Period 2 i.e. Weeks 7 through 9; ± 3 days) of Cystagon every 6 hours; or Treatment Arm B – 3 weeks (± 3 days) treatment with Cystagon every 6 hours followed by crossover to 3 weeks (± 3 days) of RP103 every 12 hours. Patients were stratified based on their WBC cystine level during the Run-in Period: Group L with ≤ 1.0 nmol/ $\frac{1}{2}$ cystine/mg protein and Group H with >1.0 and ≤ 2.0 nmol/ $\frac{1}{2}$ cystine/mg protein. It is to be noted that RP103 was administered in 25 mg and 75 mg capsules while Cystagon was administered in 50 mg and 150 mg capsules.

There were four amendments of the protocol during the course of the trial. 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.

Figure 2: Schematic of PR103-03 Trial Design



(Source: Sponsor's Summary of Clinical Efficacy, Figure 1)

B. 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)

C. 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

D. 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.

E. Treatment

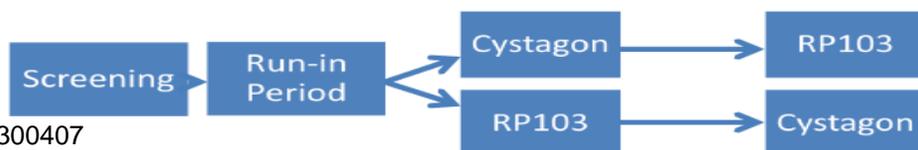
This trial was comprised of a one-week screening period, 3-week run-in period and two 3-week treatment periods.

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.

F. Concomitant Medications

There were no restrictions on the use of other concomitant medications during the trial with the exception of GAR medications. Patients who used gastric acid reducing (GAR) medications prior to the trial were permitted to continue these medications while receiving Cystagon. However, when patients' were switched to RP103 (test drug) they were requested to stop taking GAR medications at least 12 hours before receiving RP103 and to refrain from their use until completion of treatment with RP103. However, at the investigator's discretion, patients were allowed to take these medications in cases of "intolerable" gastric upset.

G. Prohibited Medications

Illegal drug use and alcohol use were prohibited during the study. The use of GAR medications is discussed above.

H. 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.

I. 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 4: 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 trial and two patients who did not meet the WBC cystine level criteria for the PP population (see primary clinical review for details).

Medical Officer's 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).”⁷ 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 (the 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.

Reviewer’s Comment:

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, (as discussed in Section 6.2 Additional Efficacy Issues/Analyses)

⁷ See the guidance for industry *Applications Covered by Section 505(b)2* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>)

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).⁸

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 pediatric patients with nephropathic cystinosis treated with a cysteamine 12-hour delayed-release formulation as the ⁹. 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 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 ± 0.22 nmol $\frac{1}{2}$ cystine/mg protein.

Reviewer’s Comment:

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.¹⁰ 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

8 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.

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

10 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).

children to swallow over-encapsulated capsules) and the inability to mask the sulfurous smell of drug metabolites that are excreted via the lungs.¹¹

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.

J. 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.

K. 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 5: RP103-03 Major Protocol Deviations lists the major protocol deviations.

¹¹ Besouw M, Blom H et al, The origin of halitosis in cystinotic patients due to cysteamine treatment, *Mol Genet Metabol* 2007; 91: 228-233.

Table 5: 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

Review of Efficacy for PR103-03

Efficacy Summary

RP103-03 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 (immediate release formulation), with a total of 8 clinical sites; 3 in the USA and 5 in Europe. To be enrolled into the study, patients must have been on a stable dose of Cystagon considered sufficient to maintain their WBC cystine level at ≤ 2.0 nmol/ $\frac{1}{2}$ cystine/mg protein. This stable dose, determined during a one week screening period (i.e. Week 1), was consequently unique for each patient.

The study consisted of two treatment periods: Period 1 (Weeks 4 through 6; ± 3 days) and Period 2 (Weeks 7 through 9; ± 3 days). Prior to treatment, eligible patients underwent a 2 week Run-in Period (Weeks 2 through 3) of Cystagon administered every 6 hours. Available safety data and WBC cystine levels collected during this Run-in period were reviewed to confirm study eligibility. On Week 3, Day 7, patients (who had their eligibility confirmed) were randomized (in an open-labeled fashion and on a 1:1 ratio, in accordance with a computer-generated central randomization schedule) to one of two treatment sequences: Treatment Arm A – 3 weeks (Period 1 i.e. Weeks 4 through 6; ± 3 days) treatment with RP103 every 12 hours followed by crossover to 3 weeks (Period 2 i.e. Weeks 7 through 9; ± 3 days) of Cystagon every 6 hours; or

Treatment Arm B – 3 weeks (± 3 days) treatment with Cystagon every 6 hours followed by crossover to 3 weeks (± 3 days) of RP103 every 12 hours. Patients were stratified based on their WBC cystine level during the Run-in Period: Group L with ≤ 1.0 nmol/ $\frac{1}{2}$ cystine/mg protein and Group H with > 1.0 and ≤ 2.0 nmol/ $\frac{1}{2}$ cystine/mg protein. It is to be noted that RP103 was administered in 25 mg and 75 mg capsules while Cystagon was administered in 50 mg and 150 mg capsules.

Forty-three patients were randomized to one of the two treatment sequences, 41 patients completed the trial, the per-protocol population (PP). There were only two patients who dropped out of this study hence missing data did not impact the study results. The mean age in the PP was 12 years, 23 (59%) were 6 to 12 years of age, 13 (33%) were 13 to 17 years of age and 3 (8%) were ≥ 18 years of age. The utilization of the applicant defined analysis sets is acceptable per ICH E9. Specifically, the utilization of the PP analysis set as the primary analysis set is acceptable as this is a non-inferiority study. There is no significant imbalance between the treatment sequences regarding the presented demographic and baseline characteristics. It is to be noted that this patient sample consisted primarily of Caucasians who were less than 18 years old (93%).

The trial results established non-inferiority of RP103 compared to Cystagon based on the PK analysis. 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.

a. Primary Efficacy Endpoint.

The results of the primary efficacy analysis (non-inferiority comparison of RP103 to Cystagon in terms of WBC cystine levels) show that non-inferiority was proven. The mean WBC cystine level was less than 1 nmol ½ 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

The applicant also provided a semi-logarithmic plot of WBC cystine concentrations versus time 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).

b. 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.¹²

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.¹³ 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 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.

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

12 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

13 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.

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.¹⁴

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.

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.

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

¹⁴ McGrath PA, Seifer CE et al., A new analogue scale for assessing children's pain: an initial validation study, *Pain* 1996; 64:435-443.

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.

c. Drug Dose Response Relationship

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

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 4.3 Preclinical Pharmacology/Toxicology, 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.

d. Subpopulations

Efficacy was assessed by gender, and it was found that the results were consistent across the female and male subgroups. The majority of randomized patients (i.e. 93%) were Caucasians who were less than 18 years old. Hence race and age specific subgroup analyses would not be informative. Due to this lack of representation, extrapolation of these study results to patients who are not Caucasian or not less than 18 years old should be made with caution.

5.3.4 RP103-04 (Extension study)

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.

Review of Efficacy for PR103-04

Efficacy Summary

The trial results indicated that patients maintain reductions in WBC cystine levels <1 nmol ½ 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 to <1 nmol ½ 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).

a. 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 newly enrolled into RP103-04 (red data points in graph).¹⁵ 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

¹⁵ 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).

to be >1 nmol $\frac{1}{2}$ 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 $\frac{1}{2}$ 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).

Reviewer Comments:

Patients enrolled from RP103 appeared to maintain reductions in WBC cystine levels < 1 nmol $\frac{1}{2}$ cystine/mg protein with long-term RP103 treatment (i.e., WBC cystine level < 1 nmol $\frac{1}{2}$ cystine/mg protein). 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 a clinically meaningful reduction in 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.

6 Review of Efficacy

Overall Efficacy Summary

Due to the orphan nature of this disease, there was only one small clinical safety and efficacy study conducted by the sponsor prior to RP103-03. This was pilot study RP103-01 which had nine patients in total, and was a single-dose, open-label and non-randomized clinical trial. In addition to study RP103-01, literature references, prominently the Dohil, Fidler et al. (2010) study) were primarily used to inform the design of this pivotal clinical trial. The Dohil, Fidler reference was a small (7 patients) trial comparing Cystagon with an enteric coated formulation of cysteamine, which showed a mean of 0.7 nmol $\frac{1}{2}$ cystine/mg protein. This along with the generally recognized clinical target of >1 nmol $\frac{1}{2}$ cystine/mg protein was used as the basis of developing the non-inferiority margin of 0.3 nmol $\frac{1}{2}$ cystine/mg protein.

It is also noted that the applicant did submit this trial protocol under IND 103,694 as a Special Protocol Assessment (SPA) to be evaluated by DGIEP. However, Raptor eventually withdrew the SPA in order to proceed with the trial due to, at that time, no

SPA agreement from DGIEP in addition to trying to meet company clinical development timelines.

The efficacy of RP103 was principally demonstrated in the single pivotal trial (RP103-03). RP103-03 was a 9-week, open-label, multicenter, randomized, cross-over, pharmacokinetic (PK) and pharmacodynamics (PD), non-inferiority (margin - 0.3 nmol $\frac{1}{2}$ cystine/mg protein) trial designed to evaluate the safety and efficacy of RP103 (cysteamine bitartrate delayed release capsules) compared to Cystagon (immediate release formulation) (with a total of 8 clinical sites; 3 in the USA and 5 in Europe). To be enrolled into the study, patients must have been on a stable dose of Cystagon considered sufficient to maintain their WBC cystine level at ≤ 2.0 nmol/ $\frac{1}{2}$ cystine/mg protein. This stable dose, determined during a one week screening period (i.e. Week 1), was consequently unique for each patient.

The study consisted of two treatment periods: Period 1 (Weeks 4 through 6; ± 3 days) and Period 2 (Weeks 7 through 9; ± 3 days). Prior to treatment, eligible patients underwent a 2 week Run-in Period (Weeks 2 through 3) of Cystagon administered every 6 hours. Available safety data and WBC cystine levels collected during this Run-in period were reviewed to confirm study eligibility. On Week 3, Day 7, patients (who had their eligibility confirmed) were randomized (in an open-labeled fashion and on a 1:1 ratio, in accordance with a computer-generated central randomization schedule) to one of two treatment sequences: Treatment Arm A – 3 weeks (Period 1 i.e. Weeks 4 through 6; ± 3 days) treatment with RP103 every 12 hours followed by crossover to 3 weeks (Period 2 i.e. Weeks 7 through 9; ± 3 days) of Cystagon every 6 hours; or Treatment Arm B – 3 weeks (± 3 days) treatment with Cystagon every 6 hours followed by crossover to 3 weeks (± 3 days) of RP103 every 12 hours. Patients were stratified based on their WBC cystine level during the Run-in Period: Group L with ≤ 1.0 nmol/ $\frac{1}{2}$ cystine/mg protein and Group H with > 1.0 and ≤ 2.0 nmol/ $\frac{1}{2}$ cystine/mg protein. It is to be noted that RP103 was administered in 25 mg and 75 mg capsules while Cystagon was administered in 50 mg and 150 mg capsules.

Forty-three patients were randomized to one of the two treatment sequences, 41 patients completed the trial, the per-protocol population (PP). There were only two patients who dropped out of this study hence missing data did not impact the study results. The mean age in the PP was 12 years, 23 (59%) were 6 to 12 years of age, 13 (33%) were 13 to 17 years of age and 3 (8%) were ≥ 18 years of age. The utilization of the applicant defined analysis sets is acceptable per ICH E9. Specifically, the utilization of the PP analysis set as the primary analysis set is acceptable as this is a non-inferiority study. There is no significant imbalance between the treatment sequences regarding the presented demographic and baseline characteristics. It is to be noted that this patient sample consisted primarily of Caucasians who were less than 18 years old (93%).

The primary endpoint and non-inferiority margin were ultimately accepted as reasonable by the review team, and the estimated sample size was confirmed by the statistical reviewer based on the assumptions provided by the applicant (See statistical review by Behrang Vail Section 3.2.1). The open-label nature of the study was acceptable due to the rationale that over encapsulating the capsules would make them larger than was feasible for children to swallow. Also the objective laboratory measuring of the endpoint itself introduced little, if any, bias. The justification of not instituting a washout period during the crossover was also deemed acceptable due to the short half-life of the drug and the need for continuous dosing to prevent deterioration of the patients clinical status.

The upper two-sided 95.8% CI limit (i.e. 0.1464) is less than 0.30 (with the associated one-sided test p-value being less than 0.02104) and hence non-inferiority can be concluded. These analyses were all re-conducted (by the statistical reviewer, Behrang Vail) utilizing the modified intent to treat (mITT) and All-Randomized analysis sets with no changes to the conclusions. In fact, the results using the PP analysis set were the most conservative i.e. the upper limit of the 95.8% CI was less than 0.1464 when using the mITT and All-Randomized analysis sets. In addition, for sensitivity analysis purposes, different covariance matrix structures were explored (by the statistical reviewer) i.e., first order auto-regressive, compound-symmetry, and unstructured, with no changes to the conclusions. No one site influenced/drove the trial results. The overall trial conclusions were not affected by the central laboratory measurement error (as discussed in section 6.1 Data and Analysis Quality below) as the originally reported two-sided 95.8% CI of the Difference in LS Means was (-0.0065, 0.1683).

Patients who enrolled in the RP103-04 open-label extension trial after completing the RP103-03 study (N=40) have low, well-maintained mean WBC cystine levels at trial entry and have continued to have low, well-maintained mean WBC levels up through Month 19 of the RP103-04 trial. In contrast, for the newly recruited patients (who had renal transplant, and were ≤ 6 years old; N=20) it was not requested, per protocol, to be previously well controlled (i.e. WBC cystine level ≤ 1 nmol/ $\frac{1}{2}$ cystine/mg protein) under Cystagon prior to trial participation. Consequently, the investigators are currently adjusting the dose of RP103 for these patients, as it is standard of care with cysteamine treatment, after starting at a RP103 daily dose of 70% of their previous daily dose of Cystagon.

In summary, in the pivotal trial, RP103 was determined to be non-inferior to Cystagon with regard to steady-state cysteamine-trough WBC cystine levels. There were no statistical issues that impacted the overall conclusions of trial RP103-03. The study's design was adjudicated as being adequate, and the applicant's corresponding analysis plan was deemed appropriate. The only potential statistical issue pertains to the study's non-inferiority margin. Unfortunately, it was not feasible to assess constancy and subsequent assay sensitivity when statistically evaluating this margin. This was due to the fact that this margin, and the overall design of RP103-03, was primarily informed by

the results of literature references and the one small pilot trial performed by the sponsor. The margin was ultimately deemed acceptable by the review team. Consequently, results from trial RP103-03 are viewed positively as the formal basis for the products' efficacy claim. The apparent sustained efficacy profile during the extension study RP103-04 further supports the efficacy claim for PROCYSBI (RP103).

6.1 Data and Analysis Quality

This study utilized Case Report Forms (CRF), and the submitted data quality and integrity appeared to be adequate upon the initial submission. However, later in the review cycle, Raptor Therapeutics, Inc. notified DGIEP that the central laboratory utilized in the study, (b) (4) made measurement errors when assessing white blood cell (WBC) cystine levels. The level of WBC cystine was utilized in the primary endpoint for this study. This initial error resulted in reported WBC cystine levels being greater than their true values. The correction of these concentration levels resulted in a numerical reduction of approximately 25% of the initially reported values. The applicant consequently submitted an updated CSR, along with updated clinical and analysis efficacy lab datasets, in order to reflect the corrected results. It was ultimately shown that the overall study conclusions were not affected by this central laboratory measurement error.

There were no issues in reproducing the primary analysis dataset (along with the numerical results presented within the updated CSR), specifically the primary endpoint, from the original data source. It was possible to verify the randomized treatment assignments, and the applicant submitted documentation of data quality control/assurance procedures within Section 9.6 of their ICH E3 compliant CSR. The applicant's statistical analysis plan (SAP) was finalized on December 6, 2010. The SAP was submitted, and all relevant analysis decisions were made before trial completion (June 3, 2011) and the planned interim analysis (January 17, 2011). Database hard-lock was on June 17, 2011.

6.2 Additional Efficacy Issues/Analyses

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 to assess the protein content of the WBC's. This can result in variations the absolute value of the WBC cystine level as much as one-half to twice the absolute value.

Reviewer Comment:

The testing for WBS cystine levels were all performed in a central lab for the controlled pivotal trial and 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 cysteine level of < 1 nmol ½ cysteine/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.

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 (>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. This association was not supported by analysis of the AE profile of both treatment groups.

For the extension trial (RP103-04), the applicant reported that 25/60 (44%) patients experienced events considered to be related to the use of RP103. Based on the primary Medical Officer's independent analysis of reported adverse events; 1/72 (1.4%) individuals in the safety database experienced an anaphylactic reaction. The safety data from the open label extension trial (RP103-04) was not comprehensively analyzed

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, no major discrepancies were uncovered 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, the data appear adequate to support an indication in treatment-naïve patients as well as patients previously treated with Cystagon.

Safety data were not available for pediatric patients under 6 years old. The applicant has submitted a Proposed Pediatric Study Request (PPSR) for the evaluation of RP103 in pediatric patients (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 (with a patient package insert), proposed risk minimization activities include heightened monitoring to address potential risks (e.g., Ehler-Danlos like syndrome). The proposed pharmacovigilance plan appears adequate 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

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 Clinical Pharmacology. 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)

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.¹⁶ 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.¹⁷

16 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.

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

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.

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 reported 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. Please see primary review by Dr. Carla Epps for detailed patient narratives.

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.

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.

Reviewer Comments:

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.¹⁸ 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, and headache being the most commonly reported events (reported in $\geq 5\%$ of individuals) in all RP103 trials. In trials in healthy 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 (3 % each).

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

¹⁸ Besouw MTP, Bowker R, Cysteamine toxicity in patients with cystinosis, *J Pediatr* 2011; 159(6): 1004-1011.

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.

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 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

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.

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. 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.

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 (b) (4) the applicant proposes (b) (4)

(b) (4) Section 4.4 Clinical Pharmacology and Section 7.2.2 Explorations for Dose Response 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. These data were reviewed during this review cycle.

7.7.2 Post Marketing Pharmacovigilance

The applicant submitted a proposed pharmacovigilance plan for RP103 (see Table 6: Summary of Proposed Pharmacovigilance Activities for RP103, on page 55). The plan includes the following risk minimization activities:

Table 6: 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 post-market experience with this product.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling negotiations are under way at the time of this review.

It is recommended 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.

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)
 (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

Pharmacology/Toxicology Labeling Recommendations

- **Changes to “Full Prescribing Information”**

(b) (4)

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

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). From a clinical reviewer opinion, the information is acceptable to support labeling from a clinical perspective as well.

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/s/

LARA DIMICK-SANTOS
04/29/2013

ANDREW E MULBERG
04/29/2013