

## CLINICAL REVIEW

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Established Name RP103 (delayed-release cysteamine bitartrate)  
Trade Name Procysbi  
Therapeutic Class Cystine-Depleting Agent  
Applicant Raptor Pharmaceuticals

Formulation(s) Extended-release oral capsules,  
25 mg and 75 mg  
Dosing Regimen (b) (4) dose: 1.3 grams/m2/day, administered in 2  
doses/day at 12 hour intervals; individual dose  
titration based on WBC cystine level  
Indication(s) Treatment of nephropathic cystinosis  
Intended Population(s) Adults and children  $\geq$  2 years old with  
nephropathic cystinosis

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

The clinical reviewer recommends approval of Procysbi (delayed-release cysteamine bitartrate) for the treatment nephropathic cystinosis in patients ages 2 to 6 years as proposed in NDA 203389 Supplement 10. Approval of NDA 203389/S-10 would expand the current indication for adults and children ages 6 years and older to include patients  $\leq 2$  years old. This reviewer recommends the same Procysbi dosing regimen for patients ages 2 to 6 as the currently approved dosing regimen for patients 6 years of age and older. For patients initiating treatment with cysteamine bitartrate, the recommended starting maintenance dosage is 1.3 grams/m<sup>2</sup> body surface area/day in two divided doses administered every 12 hours. For patients switching from immediate-release cysteamine bitartrate (i.e., Cystagon), the recommended Procysbi daily dose is (b) (4) release cysteamine bitartrate, (b) (4). For all patients, dose increases are recommended to maintain white blood cell (WBC) cystine levels within the therapeutic target range, which is usually  $<1$  nmol  $\frac{1}{2}$  cystine/mg protein, based on individual laboratory assays.

(b) (4)

### 1.2 Risk Benefit Assessment

The overall safety profile of Procysbi in RP103-04 was comparable to those seen in other trials of cysteamine formulations. In the subgroup of patients  $\leq 6$  years old, there were no serious or unexpected adverse reactions. In addition, the longer term safety data provided for clinical trial patients over 6 years of age were consistent with the current Procysbi prescribing information. Detection of rare adverse events is unlikely in this small clinical trial population (n=59), of which 13 patients were  $\leq 6$  years old. As a 505(b)(2) NDA, Procysbi approval has relied upon previous findings of both safety and effectiveness for the listed drug Cystagon (immediate-release cysteamine bitartrate), and the current product labeling for both Cystagon and Procysbi include information identified over the 20 years of post-marketing experience with Cystagon. This reviewer considers the current Procysbi data insufficient to conclude that the safety profile of Procysbi differs significantly from the immediate-release cysteamine bitartrate formulation.

Using extrapolation of efficacy from patients with nephropathic cystinosis over 6 years of age,

and data from 13 patients ages 2 to 6 years old who received Procysbi treatment in a single-arm extension study, this reviewer concludes that these data provide sufficient evidence that Procysbi treatment using the recommended dosing can maintain WBC cystine levels within the therapeutic target range in patients  $\geq 2$  years old. In addition, the clinical trial data demonstrate the feasibility of administering the approved Procysbi dosage form to patients of this age group. Therefore, this reviewer considers the risk-benefit assessment of Procysbi favorable for the proposed patient population.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

A Risk Evaluation and Mitigation Strategies (REMS) program is not recommended.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

There are no recommended clinical postmarketing requirements or commitments.

## **2 Introduction and Regulatory Background**

Cystinosis is a rare, autosomal recessive disorder (estimated incidence of 1 in 100,000 to 200,000 live births), characterized by lysosomal accumulation of cystine caused by defective transport of cystine out of lysosomes.[1] This metabolic defect is caused by mutations in *CTNS* gene, which encodes the lysosomal membrane transport protein (cystinosin) responsible for the carrier-mediated efflux of the disulfide amino acid, cystine.[2] In normal tissues, lysosomal cystine, which is formed as a bi-product of protein hydrolysis, is transported to the cytoplasm and rapidly reduced to cysteine. In cystinosis, stored cystine is poorly soluble and crystallizes within the lysosomes of many cell types, leading to tissue and organ damage.[3]

The nephropathic form of cystinosis is a multisystem disease and accounts for approximately 95% of cystinosis cases. Although kidney dysfunction is the predominant feature of nephropathic cystinosis, cystine crystals can be found on pathologic analysis of most tissues of cystinosis patients, including the conjunctivae, corneas, liver, spleen, lymph nodes, kidneys, thyroid, intestines, rectal mucosa, muscle, brain, macrophages, and bone marrow.[4] In fibroblasts and lymphocytes isolated from patients with cystinosis, lysosomal cystine concentration may reach levels 100-fold higher as those of normal individuals. However, both clinical and in vitro studies have failed to demonstrate an association between lysosomal cystine levels and disease severity, particularly in the kidney.[5] Cytotoxic mechanisms, resembling mitochondrial cytopathies, have also been implicated in the pathogenesis of cystinosis-related renal tubulopathy. These include abnormal cellular energy metabolism, oxidative stress, altered autophagy, and increased apoptosis.[6-8]

The early manifestations of nephropathic cystinosis are exclusively due to renal Fanconi syndrome, a generalized renal proximal tubular dysfunction, characterized by impaired reabsorption of water, electrolytes, bicarbonate, glucose, phosphate, carnitine, amino acids, and

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tubular proteins. Polyuria is a hallmark finding of cystinosis, whereby patients have obligate losses of large volumes of dilute urine, commonly misdiagnosed as nephrogenic diabetes insipidus.[5] Other early symptoms, also due to inappropriate renal losses of fluids and electrolytes, include vomiting, feeding difficulties, growth failure, and rickets.[9] Patients may also present with life-threatening complications of Fanconi syndrome, such as hypocalcemic seizures and tetany, hypokalemia-induced cardiac dysfunction, hypovolemic shock, or profound hypochloremic metabolic acidosis.[5,10] Definitive diagnosis of cystinosis can be made by measurement of intracellular cystine content, using a laboratory assay of elevated white blood cell cystine concentration (normal <0.2 nmol half-cystine/mg protein vs. levels >2 nmol half-cystine/mg protein in patients with nephropathic cystinosis). [9,11] A diagnosis can also be confirmed by demonstration of corneal cystine crystals by slit lamp exam or genetic analysis of the CTNS gene. [12]

In most patients with cystinosis, renal tubular damage is present at the time of diagnosis and is largely irreversible.[some Gahl, 13] Although patients' glomerular filtration rate is generally well-preserved early in the disease course, glomerular function gradually deteriorates, typically progressing to end stage renal disease by early in the second decade of life (mean age 9.6 years).[14] Beginning in the latter half of the first decade of life, involvement of other organ systems may become apparent. The most common non-renal manifestations are summarized in Table 1. Patients with cystinosis also commonly have impaired sweat production with susceptibility to heat intolerance, as well as reduced saliva and tear production. The pathophysiology of these abnormal secretory processes is unclear and glands appear morphologically normal.[15] Other less common disease manifestations include liver disease, which may present as hepatosplenomegaly with or without portal hypertension and/or hypersplenism; bone marrow dysfunction; and destructive bone lesions mimicking osteoblastic metastases, caused by abnormal endochondral ossification.[16-19]

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*Source: Gahl et al., NEJM 2002[3]*

Before renal transplantation became available, patients with cystinosis died during childhood due to end stage renal disease. Renal transplantation addressed the renal manifestations of nephropathic cystinosis and improved patient survival. However, ongoing cystine accumulation in extra-renal tissues can lead to the development of life-threatening complications, including distal vacuolar myopathy, pulmonary dysfunction, impaired swallowing, and central nervous system deterioration.[5,20]

The introduction of cysteamine ( $\beta$ -mercaptoethylamine), an orally-administered cystine-depleting sulfhydryl agent, provided patients with the first systemic therapy to address the underlying metabolic defect of cystinosis. Cysteamine is a free thiol which effectively reduces tissue cystine levels by converting intralysosomal cystine into alternate disulfides which can exit the lysosome via mechanisms independent of the defective cystinosis protein. [21] (see Section 4.4.1 for additional information regarding mechanism of action) Following ingestion of cysteamine, white blood cell (WBC) cystine content rapidly decreases after cysteamine ingestion, but rapid return to pre-dose levels without strict repeated dosing. [22]

Diligent, life-long treatment with cysteamine has been shown to substantially improve clinical outcomes in patients with cystinosis. Although cysteamine does not reverse the proximal tubular dysfunction of Fanconi syndrome, early initiation of treatment and strict maintenance of WBC cystine levels below the upper limit for asymptomatic heterozygotes, usually defined as levels  $<1$  nmol  $\frac{1}{2}$  cystine/mg protein, can effectively slow the progression of glomerular damage and delay or occasionally prevent the need for renal transplantation. [3,21,23] Routine WBC cystine measurements are recommended to evaluate disease control and guide dose adjustments.[12] The importance of early and sustained treatment is underscored by calculations reported by

Markello et al., which estimate that each month of cysteamine treatment prior to 3 years of age translates into 14 months of preserved renal function.[24] Furthermore, progression to end stage renal disease following early initiation of therapy can often be attributed to suboptimal dosing and/or poor treatment compliance.[21]

Cysteamine treatment has also positively impacted non-renal complications of cystinosis. Well-treated patients experience improved growth, and implementation of life-long therapy with cysteamine has decreased the rate of other complications, including swallowing dysfunction, myopathy, encephalopathy, pancreatic insufficiency, and, to a lesser extent, pulmonary dysfunction and hypothyroidism.[20,26-29] Consequently, cysteamine treatment is recommended even in patients who have undergone renal transplantation.[12]

Unfortunately, cysteamine treatment does not ameliorate all complications of cystinosis. Notably, the incidence of primary hypogonadism in male patients and infertility due to azoospermia remain unchanged despite adequate treatment.[30] Furthermore, because systemic administration of cysteamine does not prevent corneal crystallization, patients also require treatment with topical cysteamine eye drops.[31]

Treatment noncompliance with cysteamine is common and represents a significant obstacle to patient management. Patients cite its foul odor and taste, gastrointestinal side effects (e.g., nausea, vomiting, abdominal pain), and production of unpleasant breath and body odors as major reasons for discontinuing treatment.[3, 32] Since even brief interruptions in therapy can result in tissue damage due to rapid reaccumulation of intracellular cystine and irreversible tissue damage [33], poor tolerability and patient compliance with cysteamine treatment often interferes with optimal cystinosis management.[33,34]

## 2.1 Product Information

Procysbi (cysteamine bitartrate) is an oral, delayed-release cystine-depleting agent, approved by the FDA in 2013 for the management of nephropathic cystinosis in adults and children ages 6 years and older. Procysbi was approved under the 505(b)(2) regulatory pathway, which relied on proprietary safety and efficacy data of the listed drug, Cystagon (NDA 020392), an immediate-release formulation of cysteamine bitartrate approved by the FDA in 1994. In this sNDA, the Applicant proposes to broaden the Procysbi treatment indication to include children 2 to 6 years of age.

Procysbi is a capsule containing enteric-coated, microspherized (b) (4) beads of cysteamine bitartrate encapsulated blue hard gelatin capsules. For patients unable to swallow capsules, the capsule contents may be sprinkled onto/into one of the specified foods or liquids (see Table 14, Section 5.3). The daily dose of Procysbi is administered in 2 divided doses per day given 12 hours apart.

All cysteamine salts and formulations should be started at a low dose (1/6 to 1/4 of the goal maintenance dose) in order decrease the incidence of treatment-limiting adverse reactions and

increased progressively over 4–6 weeks to reach a target dose of 1.3 grams/m<sup>2</sup> for patients up to (b)(4) 50 kg, and 2 g/day for patients weighing more than 50 kg. WBC cystine levels should be monitored to assess the adequacy of cystine depletion, and the dose should be adjusted to achieve levels below the upper limit of the local reference values for heterozygous individuals (commonly defined as <1 nmol ½ cystine/mg protein). The maximum dose should not exceed 1.95 g/m<sup>2</sup>/day.

## 2.2 Tables of Currently Available Treatments for Proposed Indication

**Table 2: Currently Available Treatments for Proposed Indication**

Drug	Formulation	Approved Indication	Dosage <sup>a</sup>
Cystagon (cysteamine bitartrate, immediate-release) Approved 1994	50 mg & 150 mg capsules for oral administration	Management of nephropathic cystinosis in children & adults	<ul style="list-style-type: none"> <li>• Administration of total daily dose in 4 divided doses, given every 6 hours</li> <li>• Age ≤12 yr: 1.3 grams/m<sup>2</sup>/day</li> <li>• Age &gt;12 yr and &gt;50 kg (110 lbs): 2 grams/day</li> </ul>
Procysbi (cysteamine bitartrate, delayed-release) Approved 2013	25 mg & 75 mg capsules for oral administration	Management of nephropathic cystinosis in adults & children 6 years and older	<ul style="list-style-type: none"> <li>• Administration of total daily dose in 2 divided doses, given every 12 hours</li> <li>• Cysteamine-naïve patients:<sup>b</sup> <ul style="list-style-type: none"> <li>≤110 lbs<sup>c</sup>: 1.3 grams/m<sup>2</sup>/day</li> <li>&gt;110 lbs<sup>c</sup>: 2 g/day</li> </ul> </li> <li>• Patients switching from Cystagon: same total daily dose as Cystagon dose</li> </ul>

<sup>a</sup> These are recommended initial maintenance dosages. For both Cystagon and Procysbi, drug dosage should be titrated to achieve adequate intracellular cystine depletion.

<sup>b</sup> Note that clinical trials of Procysbi did not enroll cysteamine-naïve patients.

<sup>c</sup> or 50 kg

## 2.3 Availability of Proposed Active Ingredient in the United States

Cysteamine is the only available treatment of nephropathic cystinosis, and its bitartrate salt is the only marketed form in the United States. Cysteamine bitartrate is the active ingredient in two FDA-approved products— Cystagon, an immediate-release formulation (NDA 020392, approved August 15, 1995) manufactured by Mylan Pharmaceuticals, and this delayed-release formulation (Procysbi NDA 203389). Procysbi was approved by the FDA on April 30, 2013 under a 505(b)(2) NDA, with Cystagon as the listed drug. At the time of this review, there are no drug shortages for either product.

Cysteamine (as cysteamine hydrochloride) is also available in the U.S. as a topical ophthalmologic solution (trade name Cystaran, NDA 200740, approved October 10, 2012) for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

## 2.4 Important Safety Issues with Consideration to Related Drugs

Across clinical trials of cysteamine, gastrointestinal (GI) disorders account for the largest group



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of the most frequently reported adverse reactions. The common GI symptoms associated with cysteamine treatment include nausea, vomiting, anorexia and abdominal pain; however severe manifestations, such as GI ulceration and bleeding, can occur, and are included in the Warnings and Precautions section of the Procysbi label. Cysteamine is a known ulcerogenic compound and has been used to induce gastrointestinal injury in animal ulcer studies. [35] The pathogenesis of cysteamine-induced GI ulceration is likely the cumulative effect of several of drug-induced changes in GI physiologic mechanisms, including increased gastrin and gastric acid production, inhibition of somatostatin, delayed gastric emptying, and decreased bicarbonate and gastric mucus production.[36] Significant increases in gastric acid production and serum gastrin level have been demonstrated in cystinosis patients following administration of cysteamine bitartrate [36,37], and reported peak gastrin levels are similar after administration of Procysbi and immediate-release cysteamine bitartrate (Cystagon). Elevated gastrin levels have also been shown to correlate with the onset of gastrointestinal symptoms (e.g., nausea, vomiting, retching, abdominal pain, and heartburn), and acid suppression therapy with proton pump inhibitors was associated with reductions in both gastric acid output, gastrointestinal symptoms, and ulcer formation.[21,36.37]

The current Procysbi prescribing information has warnings/precautions for 6 serious adverse reactions—gastrointestinal ulcers and bleeding (described above), central nervous system (CNS) symptoms, Ehlers-Danlos-like syndrome, severe skin rashes, leukopenia and elevated alkaline phosphatase levels, and benign intracranial hypertension. For 5 of the 6 serious adverse reactions, including gastrointestinal ulcers and bleeding, the Procysbi product labeling specifies that the reaction (n=4) or its most serious manifestations (n=1) is associated with use of immediate-release cysteamine bitartrate.

(b) (4)

CNS symptoms have also been presented as an adverse reaction to cysteamine [45-47], with characteristics that appear to distinguish between disease-related and treatment-related complications. The risk of CNS events in patients with nephropathic cystinosis and relevant issues to this supplemental application are discussed further in Section 7.3.5 (Submission-Specific Primary Safety Concerns).

Other significant adverse reactions to cysteamine include severe hypersensitivity reactions, including anaphylaxis and Stevens Johnson syndrome. Because of the risk of cross-reactivity with another thiol, penicillamine, cysteamine bitartrate is also contraindicated in patients with known hypersensitivity to penicillamine. The most frequently reported side effects of cysteamine are unpleasant breath and sweat odor, and although they are not associated with significant morbidity, they are major contributors to medication non-compliance and have been implicated in the poor outcomes of many patients. [33,34,48]

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

- April 30, 2013: FDA approval of the 505(b)(2) NDA for Procysbi, with Cystagon as the listed drug (refer to Clinical Review by Carla Epps dated April 26, 2013 for details of regulatory activity prior to original NDA submission)
- August 19, 2013: Written Request for Pediatric Studies issued to the applicant by the FDA (b) (4)



- February 19, 2014: Type B Pre-NDA meeting held at the request of the Applicant to discuss October 31, 2013 submission deficiencies and the Applicant's plans for sNDA re-submission
- July 14, 2014: Submission of supplemental NDA consisting of the same proposals and supporting clinical trial data as the October 31, 2013 submission (see above). This applicant was (b) (4) assigned (b) (4) NDA 203389 (b) (4) S-010, (b) (4) which were evaluated during this review cycle and reviewed in this report.

## 2.6 Other Relevant Background Information

On September 12, 2013, Procysbi received marketing authorization by the European Commission (EC), following the positive recommendation by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) in June 2013. Procysbi received orphan medicinal product designation from the EMA, which provides a 10-year period of market exclusivity in the European Union.

A major amendment was received on March 2, 2015, which required an extension of the review period for (b) (4) efficacy supplement (b) (4) to permit review of the additional information.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

This was an electronic submission in eCTD format. NDA elements were located in two different electronic submissions— (1) reports from studies which provided data to support this sNDA, along with their supporting datasets, data tables, and documentation were located in the previous submission dated October 31, 2013 (see Section 2.5), and (2) integrated clinical summaries, along with their supporting datasets, data tables, and documentation were provided at the time of submission of this supplemental application, dated July 14, 2014. Despite this issue, the application was generally well-organized and included a reviewer guide with functional links to facilitate navigation of application. The preliminary survey found the application to contain all required components, including datasets of sufficient quality to support filing of the sNDA.

However, this Reviewer identified several discrepancies between data provided in the submission dated October 13, 2013, which contained the clinical study data and reports for RP103-04 as of the data cutoff date of July 10, 2013, and the submission dated July 14, 2014, which contained the integrated clinical study data and reports. Multiple information requests were sent to clarify these discrepancies. In response, the Applicant submitted sNDA amendments (NDA eCTD sequence numbers 203389/0073 dated March 2, 2015; 0075, dated March 18, 2015; and 0077, dated April 20, 2015), which include amended clinical study reports, clinical summaries, and datasets.

During the review, the review team sent several information requests to the Applicant to obtain additional information needed to complete the review. The Applicant provided the requested data and clarifications; however, the volume of additional information and long response time necessitated filing of a major amendment to extend the review period.

#### **3.2 Compliance with Good Clinical Practices**

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

No site inspections were performed as part of the review of this sNDA. For the original NDA review, the Division of Scientific Investigations (DSI) performed inspections of two clinical sites, Site 3 (Emory University; Investigator: Larry Greenbaum) and Site 6 (Hôpital Necker-Enfants Malades; Investigator: Patrick Niaudet). These sites were selected for inspection because of their relatively high enrollment in RP103-03 and RP103-04 (one domestic and one foreign site). No significant regulatory violations were identified, and DSI concluded that data from the two sites could be used in support of the NDA.

### **Protocol Violations and Deviations**

As of the July 10, 2013 data cut-off date, 537 protocol deviations were reported for RP103-04. All but one of the 60 patients had at least 1 protocol deviation (range 0-29), and 23 patients had  $\geq$  10 protocol deviations.

Twenty-three (4.3%) of the protocol deviations were categorized as “major” protocol deviations and are listed in Table 3 by type of protocol deviation. These were reported from 7 of the 10 study sites and occurred in 16 (26.7%) patients—9 patients with 1 major deviation and 7 patients with 2 major deviations. Three major deviations were related to study participation eligibility criteria—two were violations of exclusion criteria (Subject 05004 had a screening hemoglobin  $<10$  g/dL and Subject 05005 had an ALT level  $> 2$  times the upper limit of normal within 6 months of screening), both of which received written exceptions from the Applicant, and the third was a violation of Study Stopping criteria (Subject 07003 with a serious adverse event of gastroenteritis), which was also approved by the Applicant.

**Table 3: Major Protocol Deviations for all Enrolled Patients (N=23)**

<b>Type of major deviation*</b>	<b>Major deviations (n)</b>	<b>Patients (n)</b>
Violation of eligibility criteria	2	2
Incorrect informed consent procedure	1	1
Patient medication non-compliance	3	2
Patient procedure non-compliance	2	1
Patient error in study drug dosing or administration	3	2
Procysbi unavailable- Cystagon substituted <sup>†</sup>	5	3
Non-adherence to adverse event reporting requirements by Investigator	2	2
Non-adherence to study stopping criteria by investigator	1	1
Study procedure not performed	1	1
Procedure outside protocol window	3	3

(Source: Reviewer’s table adapted and summarized from Table 6 entitled “Major Protocol Deviations (Safety Population)”, Interim Clinical Study Report pages 61-63, Module 5.3.5.2)

\* For the 23 major protocol deviations, the Applicant provided a “deviation description” and the “deviation category” assigned by Investigators. In this table, deviations were grouped by the “type of major deviation”, a designation assigned by this reviewer because “deviation category” assignments were inconsistent. These categories were created based on the deviation descriptions provided because this reviewer considered the Applicant’s deviation categories too broad to be informative.

† For 7 patients, Procysbi treatment was interrupted at least once for re-supply issues leading to study drug unavailability (total 10 interruptions). During these periods, patients were treated with Cystagon. Five of the 10 treatment interruptions (for 3 of 7 affected patients) were considered “major” protocol deviations.

537 reported protocol deviations, this reviewer considers 280 (52%) to be “clinically important”,

meaning that these deviations needed to be considered when interpreting relevant clinical trial data. The evaluation of Supplement 10 was not substantially affected by these protocol deviations because efficacy assessments relied primarily on an objective PD marker which is not significantly affected by the timing of assessments (see Figure 34 in the Appendix, Section 9.4.2). However, the interpretability of plasma cysteamine levels and efforts to assess the impact of altering Procysbi administration procedures were limited by these protocol deviations/violations and were taken into consideration during labeling discussions. (Table 4)

**Table 4: Protocol Deviations Considered Clinically Meaningful by Reviewer (N=280)**

Type of Protocol Deviation †	Deviations (n)	Patients (n)
Medication non-compliance (i.e., reported missed study drug doses)	32*	11
Incorrect dosage administered	59*	16
Incorrect number of capsules returned at visit- (suspected missed doses/dosing errors)	19	4
Incorrect administration procedures	68*	27
PK/PD assessments** ≥10 minutes outside specified time point (i.e., 30 minutes post-dose)	53	29
Missing records (incomplete/missing journals)	25	14
PK/PD assessment not performed	6	5
Procysbi unavailable- Cystagon substituted	10	7
Non-adherence to study stopping criteria by investigator	1	1
Alcohol and/or illicit drug use (prohibited per protocol)	5	1
Investigator prescribed Procysbi dose higher than instructed by protocol	2	2

(Source: Reviewer's table adapted and summarized from Table 6 entitled "Major Protocol Deviations (Safety Population)", Interim Clinical Study Report pages 61-63, Module 5.3.5.2)

† The "Type of Protocol Deviation" categories in this table were created and assigned by this Reviewer, based on the protocol deviation descriptions provided by the Applicant.

\* Multiple missed doses/incorrect doses/incorrectly administered doses may be reported in a single protocol deviation

\*\* 593 PK/PD assessments were performed during Procysbi treatment. Protocol deviations were reported for 85 (14.3%) PK/PD assessments due to sample collection outside protocol window (i.e., not collected 30 minutes post-dose)

Subject 09003 had 5 protocol deviations for alcohol and/or illicit drug, which were prohibited for study participation. Although these repeated episodes of protocol non-adherence fulfilled Study Stopping criteria, this patient was not discontinued from the study.

In addition this reviewer identified 4 screening laboratory results which likely protocol deviations/violations, baseline AST level 76 units/L (>1.5 times the upper limit of normal) in Subject 03011, and estimated glomerular filtration rate <30 mL/min/1.73m<sup>2</sup> in Subjects 03004,

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07004, and 02010.

Lastly, there were 2 patients with ongoing enrollment in RP103-04 for whom >4 months elapsed between their most recent Study Visit and data cutoff—Subject 02013 (4.4 months) and Subject 02014 (6.2 months), indicating at least 1 missed study visit per patient which were not reported by the Applicant as protocol deviations/violations.

### **Protocol Amendments**

The Applicant issued 6 amendments to RP103-04 clinical study protocol. Among the changes included in these amendments were changes to patient eligibility criteria, study medication dosing, study medication administration, and the schedule of study assessments, 8 of which led to clinically meaningful baseline differences among study patients. These differences were taken into consideration when performing clinical trial analyses. See Section 5.3 for more detailed discussion of RP103-04 Protocol Amendments, and a list of the changes which were deemed clinically relevant.

### **3.3 Financial Disclosures**

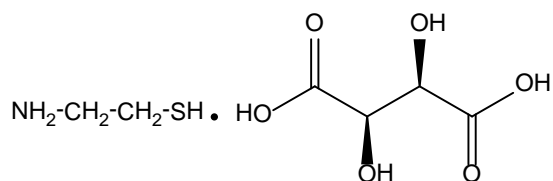
The Applicant reports that there were no financial arrangements between the Applicant and any of the clinical trial Investigators.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

Cysteamine bitartrate is a water soluble white powder with a molecular weight of 227.24 Da. The molecular weight of the free base is 77.15 Da.

The molecular formula of cysteamine bitartrate is  $C_2H_7NS \cdot C_4H_6O_6$ , with the following chemical structure:



Procysbi is available as 25 mg and 75 mg delayed-release capsules, expressed as the quantity of the free base cysteamine.

The CMC Reviewer Dr. Jean Salemmé performed a review of labeling and Environmental Assessment and concluded that both are acceptable for Supplement (b) (4) 10. An

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Environmental Assessment, or a Claim for an Exemption from performing an Environment Assessment, was (b) (4) required for Supplement 10. Because this was not included in the initial submission, an Information Request was sent and the Applicant submitted a request for categorical exclusion from the preparation of an Environmental Assessment, which was deemed adequate by the CMC reviewer. (See the CMC review dated April 17, 2014).

## 4.2 Clinical Microbiology

No clinical microbiology issues were addressed during this review.

## 4.3 Preclinical Pharmacology/Toxicology

No new nonclinical studies were conducted to support this application.

## 4.4 Clinical Pharmacology

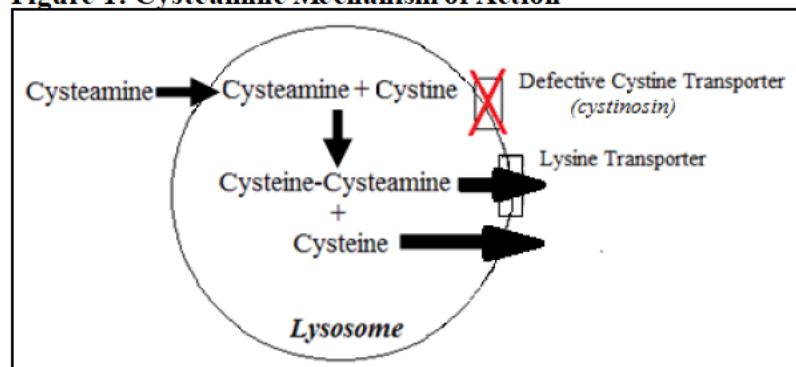
Procysbi is a hard gelatin capsule containing enteric-coated microspherized (b) (4) beads of cysteamine bitartrate, (b) (4). In clinical trials, Procysbi administered with an acidic beverage per protocol by most patients with a few documented exceptions. For patients unable to swallow capsules, the capsule contents were sprinkled onto/into one of the specified foods or liquids (see Table 7, Section 5.3). Clinical pharmacology issues addressed during this review included evaluation of (1) the proposed Procysbi dosing for patients ages 2 to 6 years, (2) the recommended Procysbi starting dosage for patients switching from immediate-release cysteamine bitartrate, (3) Procysbi administration procedures, (4) the impact of concomitant gastric acid reducing medications on the pharmacokinetics of Procysbi, (4) the use of routine pharmacokinetic (PK) assessments (i.e., cysteamine plasma level) to assess the adequacy of Procysbi dosing, and (5) the appropriate timing for routine PK and pharmacodynamic (PD) testing. The reader is referred to the Clinical Pharmacology review by Drs. Insook Kim (clinical pharmacology reviewer) and Jee Eun Lee (pharmacometrics reviewer) dated June 29, 2015. This reviewer concurs with the conclusions in their review and has summarized the important findings below. In addition, because the primary efficacy endpoint is the same as the PD measurement for clinical pharmacology analyses, and these assessments are used in clinical practice as the basis for Procysbi dose adjustments, these analyses overlap with the analyses used for clinical assessments of efficacy and dosing in this review.

### 4.4.1 Mechanism of Action

In patients with nephropathic cystinosis, lysosomal cystine accumulates as a result of defective cystinosis, the transmembrane cystine protein transporter. Cysteamine, like other amino-acid methyl esters (aminothiols), readily crosses membranes and accumulates in the lysosome due to effects of the acidic environment. Within the lysosome, cysteamine participates in a thiol-disulfide interchange reaction with cystine, yielding cysteine and cysteine-cysteamine mixed

disulfides, which, unlike cystine, are able to exit the lysosome via mechanisms independent of the cystine carrier system (Figure 1). [47, 49]

**Figure 1: Cysteamine Mechanism of Action**



(Source: Reviewer's own figure based on information in Thoene et al., 1976 [47])

Lysine transporter/cationic amino acids carrier

Defective cystine transporter=cystinosis

#### 4.4.2 Pharmacodynamics

WBC cystine concentration is a pharmacodynamic biomarker for assessing intracellular cystine depletion, which has been shown to correlate with other tissue cystine levels. [50] WBC cystine measurements are widely used in clinical practice confirm diagnosis, monitor disease control, and optimize cysteamine dosing.[3] The recommended therapeutic target range is  $<1 \text{ nmol } \frac{1}{2} \text{ cystine/mg protein}$  for most laboratories [12], and maintenance of WBC cystine levels below this level has been shown to correlate with improved clinical outcomes.[24,25]

WBC cystine was the primary efficacy endpoint for RP103-03, the randomized cross-over clinical trial used to support the approval of Procysbi, and is also the primary efficacy endpoint in this efficacy supplement to support the use of Procysbi in patients with nephropathic cystinosis ages 2 to 6 years old (Supplement 10). For a review of these data, the reader is referred to Section 6.1.4 [Analysis of Primary Endpoint(s)].

#### 4.4.3 Pharmacokinetics

During RP103-04,  $C_{30}$  plasma cysteamine levels were obtained along with WBC cystine levels at all scheduled Study Visits. Although optional PK substudy visits were added to RP103-04 study procedures for newly enrolled patients, insufficient data were obtained for evaluation of full PK profiles in these patients. The available  $C_{30}$  PK data were used to perform dose-exposure and exposure response analyses to support dosing recommendations and the use of extrapolation of efficacy, respectively.

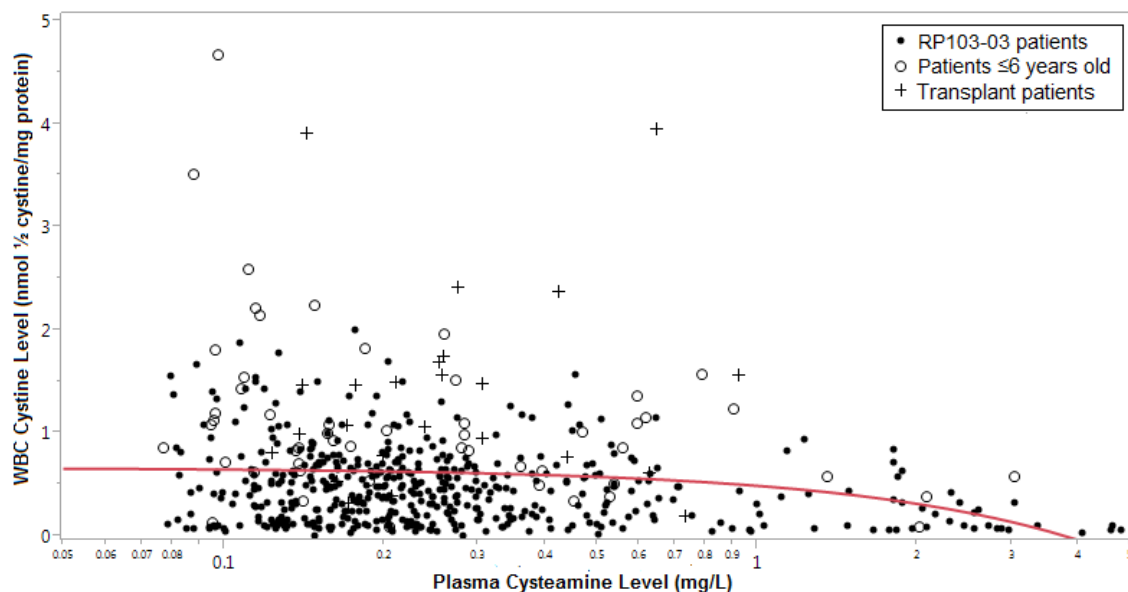
Consistent with data from study RP103-03, PK/PD analyses of RP103-04 clinical trial data demonstrated a positive relationship between plasma cysteamine levels ( $C_{30}$ ) and WBC cystine



levels, and the PD responses across cysteamine exposures in patients  $\leq 6$  years old appear to superimpose with that of the older patients. (Figure 2)

(For a review of RP103-03 clinical pharmacology data, the reader is referred to the Clinical Pharmacology review of the original 203389 NDA review by Dr. Kristina Estes dated March 30, 2012).

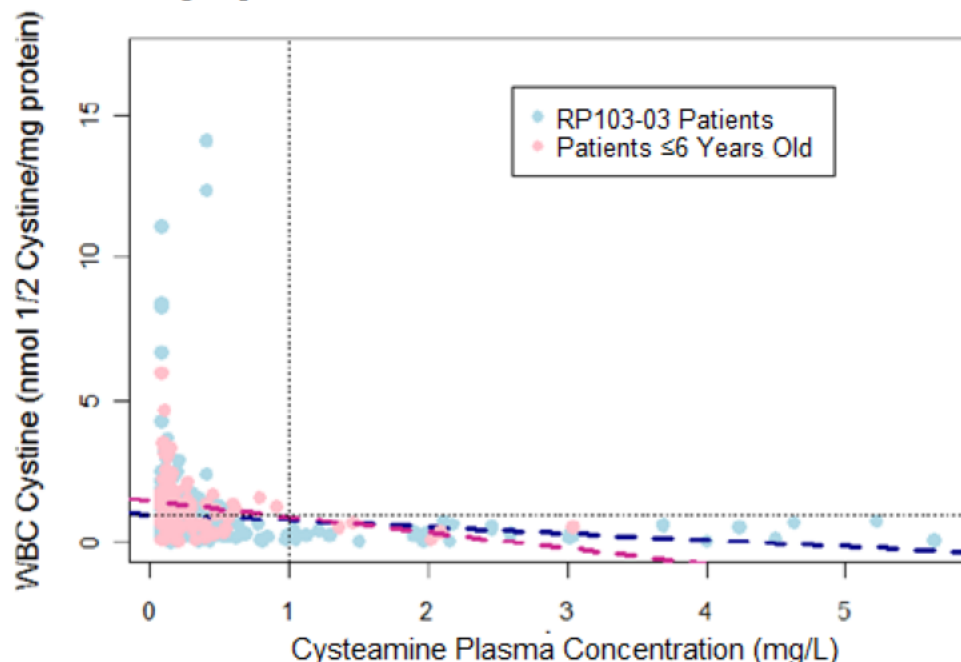
**Figure 2: Exposure ( $C_{30}$  Plasma Cysteamine Level) vs. Response (WBC Cystine Level)**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

Figure 3, generated by the Pharmacometrics Reviewer Dr. Jee Eun Lee, demonstrates overlap of the range and central tendency of exposure-response data for patients  $\leq 6$  years old and RP103-03 patients who were  $>6$  years old, though the linear regression line for the patients ages 2 to 6 years old is steeper than the RP103-03 patients. According to the Pharmacometrics Reviewer, these data should be interpreted with caution because the differences in regression lines can be explained by the higher WBC cystine levels in patients  $\leq 6$  years old.

**Figure 3: Exposure-Response with Linear Regression Lines for RP103-03 and  $\leq 6$  Year Old Patient Subgroups**



(Source: Figure 7, Clinical Pharmacology review by Dr. Jee Eun Lee dated June 29, 2015)

Based on the results of RP103-04 exposure-response analyses, the use of cysteamine plasma concentration to guide dose adjustments, in the absence of WBC cystine measurements, was re-evaluated (also discussed in Section 6.1.5, Analysis of Secondary Endpoints). The current Procysbi label states that a (b) (4) plasma cysteamine concentration can be used (b) (4) if WBC cystine levels are unavailable. The Applicant proposes to (b) (4)

(b) (4) Therefore this reviewer recommends that, consistent with international consensus guidelines [12], the label recommend only WBC cystine level as a measurement to guide Procysbi dosage adjustment.

### **Concomitant Administration of Proton Pump Inhibitors**

(b) (4) co-administration with medications that increase gastric pH, such as proton pump inhibitors (PPIs), can alter the pharmacokinetics (PK) of Procysbi. However, due to the ulcerogenic properties of cysteamine, the use of PPIs is commonly required in patients treated with cysteamine-containing medications to prevent severe gastrointestinal complications.

The effect of proton pump inhibition on the pharmacokinetics of Procysbi was evaluated in healthy subjects (n=20) in Study RP103-HLTA 009, entitled “An Open-Label, Single-Dose Study to Evaluate the Bioequivalence of Cysteamine Bitartrate Delayed-release Capsules (RP103) Following a 600 mg Dose Before and During Treatment with Omeprazole, a Proton Pump Inhibitor (PPI).”

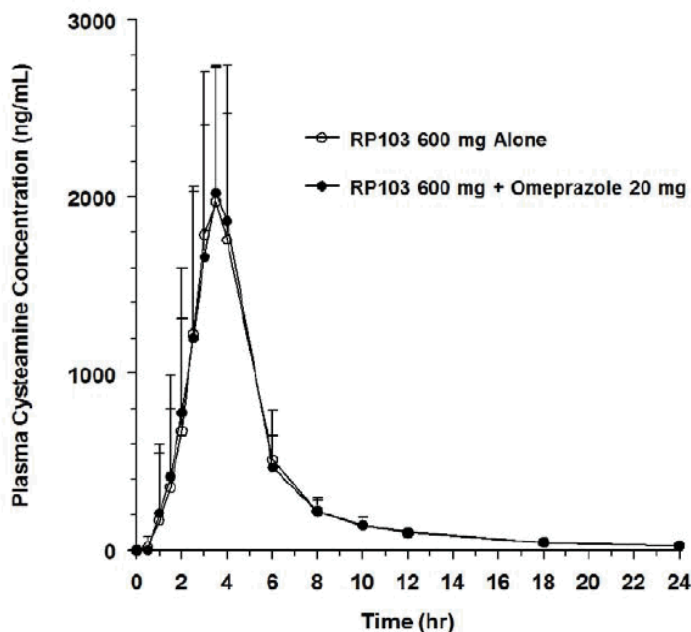
**Table 5: Study RP103-HLTA 009 Treatment Schedule**

Treatment for Period/Study Day					
Period 1	Period 2				
Day 1 Treatment A	Day 2	Day 3	Day 4	Day 5	Day 6 Treatment B
RP103 600 mg alone, taken with 240 mL orange juice	Omeprazole 20 mg, taken with 240 mL water	Omeprazole 20 mg, taken with 240 mL water	Omeprazole 20 mg, taken with 240 mL water	Omeprazole 20 mg, taken with 240 mL water	RP103 600 mg and Omeprazole 20 mg, taken with 240 mL orange juice

(Source: Applicant’s Table 1, “Treatment for Period/Study Day”, RP103-HLTA-009 Clinical Study Report, page 20/127, NDA 203389)

The pharmacokinetic profiles of Procysbi alone (day 1) and Procysbi + omeprazole (day 6) were compared. Both doses of Procysbi were administered to fasted subjects with 240 mL of orange juice. Omeprazole had no significant effect on the pharmacokinetics of Procysbi when administered in the fasted state with substantial quantities of orange juice. (Figure 4)

**Figure 4: Pharmacokinetics of Procysbi with and without Concomitant Omeprazole**



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*(Source: Applicant's Figure 1, "Arithmetic Mean (+SD) Plasma Cysteamine Concentration-Time Profiles in 20 Fasted Healthy Subjects Following a Single Oral 600 mg Dose of RP103 Capsules Given Alone and With the Fifth Consecutive Daily 20 mg Dose of Omeprazole Capsules (linear and semi-logarithmic scale)", RP103-HLTA-009 Clinical Study Report page 46/127)*

(b) (4)

### **Procysbi Administration with Acidic Beverages**

The enteric coating of Procysbi granules (Eudragit®), (b) (4)

(See the CMC review of the original Procysbi NDA 203389 by Dr. Jane Chang, dated December 17, 2013 for additional details).

Throughout Procysbi clinical trials, patients were instructed to take intact Procysbi capsules with an acidic beverage. Because Procysbi is a chronically administered medication, complying with these administration restrictions may be challenging for patients. It is unclear whether administration with water which has a neutral pH would alter the dissolution properties of the enteric coating in patients with normal gastric pH (i.e., patients not receiving gastric acid reducing medications). Patient diaries indicate that some patients may have taken their Procysbi doses with water without significant effect on their WBC cystine levels; however, no formal studies have been conducted, either in healthy individuals or patients, comparing the effects of effects of administration with water vs. orange juice on the pharmacokinetics of Procysbi.

(b) (4)

### **Administration of Procysbi with Bicarbonate- and Carbonate-Containing Medications**

The management of Fanconi syndrome and chronic kidney disease, both of which affect the majority of patients with nephropathic cystinosis, frequently includes treatment with bicarbonate- and carbonate-containing medications for disease sequelae such as acidosis, hyperphosphatemia, hypocalcemia, and osteopenia. Because these medications will acutely increase gastric pH, these medications should not be co-administered with Procysbi. Although the effect of these basic compounds on Procysbi have not been evaluated, sufficient in vitro evidence exists to inform this recommendation. Therefore, patients should ensure that Procysbi is not administered within 1 hour of these medications, and the product labeling should be amended to include this recommendation.(See Section 9.2, Labeling Recommendations)

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Study RP103-04 is the only source of new clinical trial data reviewed for this application. During the conduct of RP103-04, multiple changes to clinical trial procedures were implemented. Thus, the patients' study procedures often depended on the time of their enrollment. Table 6 shows the dates of patient enrollment for the different patient subgroup and shows the different protocol amendments in effect at the time of enrollment.

**Table 6: Dates of RP103-04 Enrollment and Current Protocol Amendments at the Time of Enrollment (N=59)**

	RP103-03 (n=40)	Newly enrolled patients	
		≤6 Years Old (n=13)	Transplant (n=6)
Enrollment dates (month and year)	August 2010- June 2011	November 2011- April 2012	December 2011- January 2012
Most recent protocol amendment in effect at enrollment	Amendment 3 (n=34)	Amendment 5 (n=19)	
	Amendment 4 (n=6)		

Source: Reviewer's own table based on Applicant's Analysis Datasets, Module 5.3.5.2)  
 Details of protocol amendments are located in Appendix, Section 9.4.3.

### 1.2 Review Strategy

NDA supplement (b) (4) 203389/ (b) (4) S-010 include multiple proposals for labeling changes submitted by the Applicant for review. The primary proposals evaluated in this clinical review are:

1. Expansion of the approved population for Procysbi treatment to include patients  $\geq 2$  years of age (Supplement 10)

(b) (4)

Other proposed labeling changes also discussed in this review are the following:

(b) (4)

The analyses and assessments for this review were performed using clinical trial data from RP103-04, an open-label, single-arm trial of Procysbi for treatment of cystinosis. This is an ongoing study; therefore, the sponsor submitted an interim report with a data cutoff date of July 10, 2013. For 40 of the 60 patients, RP103-04 is an extension study of a 9-week randomized, cross-over, non-inferiority clinical trial comparing Procysbi to

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immediate-release cysteamine bitartrate (RP103-03). An additional 20 patients were enrolled directly into this single-arm study. This Clinical Review also references data from RP103-03, which, along with efficacy data of the reference drug Cystagon (immediate-release cysteamine bitartrate), served as the basis for approval of Procysbi under 505(b)(2) of the Food, Drug, and Cosmetics Act. These references are based on the Clinical Review conducted by Carla Epps, dated April 26, 2013.

Included in this clinical review is an assessment of the safety and efficacy of Procysbi for patients 2-6 years old years, based on a sub-population of 13 “newly enrolled” patients, who, like the patients in RP103-03, had all been treated with immediate-release cysteamine bitartrate for a confirmed diagnosis of nephropathic cystinosis, a disease which manifests in infancy.[3,4] Because these patients enrolled directly into RP103-04 without completion of RP103-03, there are no data from adequate and well-controlled trials for patients in this age group. However, because these patients are expected to have similar disease progression and response to treatment as the older clinical patients, efficacy of Procysbi could be extrapolated from RP103-03 clinical trial data in the 39 “per protocol” patients, aged 6 to 26 years old, with support from RP103-04 data. For the safety evaluation in these patients, assessments are based primarily on the uncontrolled data from RP103-04. However, as a 505(b)(2) NDA, information from clinical trial and post-marketing experience with Cystagon (immediate-release cysteamine bitartrate), approved in 1994 are also considered supportive.

WBC cystine is an accepted pharmacodynamic (PD) biomarker of cystine depletion, which has been shown to correlate with long-term clinical outcomes in patients with cystinosis, regardless of age.[12] Furthermore, standard of care for cystinosis patients includes use of WBC cystine measurements to optimize cysteamine dose, regardless of the cysteamine formulation. In RP103-03 and RP103-04, Procysbi doses were based on the patients’ previous cysteamine doses and adjusted based on PD and safety assessments. According to the extrapolation guidelines [51], extrapolation of efficacy relies on the assumption of a similar exposure-response between adults and pediatric patients. However, there is an established method for dosing cysteamine based on PD measurements, regardless of age. Furthermore, intra-patient Procysbi dosage adjustment is a central feature of RP103-04, thus enmeshing dose assessments with efficacy evaluations. Therefore, analyses used to inform dosing for patients age 2 to 6 years old are intertwined with efficacy analyses in Section 6 and are discussed in Section 6.1.8.

### **5.3 Discussion of Individual Studies/Clinical Trials**

#### **RP103-04: Interim Analysis**

The first patient enrolled in Study RP103-04 on August 27, 2010, and the data cutoff date for the Interim Clinical Study Report is July 10, 2013.

#### **Title**

Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-release

## Capsules Procysbi in Patients with Nephropathic Cystinosis

### **Study Objectives**

- Primary Objective:
  - To assess safety and tolerability of long-term repeat dosing of RP103 in patients with cystinosis
- Secondary Objectives:
  - To assess the steady-state pharmacokinetics (PK) and pharmacodynamics (PD) of RP103
  - To assess patient quality of life (PedsQL™ Version 4.0 or RAND 36-item Short Form Health Survey (SF-36R) Version 2 instruments)

### **Study Design**

Study RP103-04 is an ongoing, open-label study of the safety, tolerability and steady-state pharmacokinetics and pharmacodynamics of Procysbi in patients with nephropathic cystinosis. This study was designed as an extension trial for patients who completed the Phase 3 trial, RP103-03, and wished to continue Procysbi treatment. After completion of RP103-03, enrollment in this open-label trial was opened to eligible patients less than 6 years of age and patients who had received kidney transplants.

### **Protocol Amendments**

The Applicant issued 6 protocol amendments for RP103-04. Amendments 1 through 3 were issued prior to the enrollment of the first patient in RP103-04. Enrollment was restricted to patients who completed RP103-03 until after Amendment 5.

Five of these amendments were issued prior to the original Procysbi NDA submission and have been reviewed in detail by Carla Epps (Clinical Review dated April 26, 2013). Amendment 6, dated September 26, 2012, is detailed below. For Amendments 1 through 5, the protocol changes which led to differences in patient characteristics and inconsistency in study procedures are listed in Table 7.

**Table 7: Clinically Relevant Changes to RP103-04 Study Protocol from Amendments 1-5**

<b>Amendment Number</b>	<b>Clinical Relevance (Rationale, if provided)</b>	<b>Changes to RP103-04 Protocol</b>
<b>1</b>	Amended Procysbi dosing procedures (to be consistent with RP103-03 study procedures)	For newly enrolled patients: <ul style="list-style-type: none"> <li>• Procysbi starting daily dose of 70% of previous daily Cystagon dose</li> </ul>
<b>2</b>	Modified eligibility criteria	Eliminated inclusion criterion requiring patient to be on a suitable dose of cysteamine that produces a meaningful reduction in WBC cystine levels
<b>4</b>	Modified study medication dosing (to be consistent with concurrent RP103-03 study procedures <sup>#</sup> )	For newly enrolled patients: <ul style="list-style-type: none"> <li>• Procysbi <u>starting</u> daily dose changed to 80% of previous daily Cystagon dose (from 70%, per original protocol)</li> <li>• Specified dose increase allowed during up to 100% of previous daily Cystagon dose (instead of 20-25% increase in dose)</li> </ul>
	Modified study drug administration procedures (based on results from RP103-03 demonstrating significant effects of food on Procysbi absorption)	Patients instructed to: <ul style="list-style-type: none"> <li>• Fast <math>\geq 3</math> hours prior to dosing; and</li> <li>• Ingest meal between 30 &amp; 60 minutes after dosing (changed from instructions to eat food immediately prior to dosing and withhold dairy products for 1 hour before and 1 hour after dosing, as per original protocol through amendment 3*)</li> </ul>
<b>5</b>	Modified RP103 doses (to be consistent with concurrent RP103-03 study procedures)	For newly enrolled patients, changed starting daily dose to 70% previous daily Cystagon dose (from 80% as last specified in Amendment 4)
	Modified enrollment criteria <sup>†</sup> (based on similar PK with intact and opened capsules <sup>‡</sup> )	Allowed enrollment of patients requiring administration of opened capsules either by mouth or via gastrostomy tube
	Modified study drug administration procedures (to accommodate newly eligible patients who will not be taking intact capsules)	<ul style="list-style-type: none"> <li>• Changed fasting period to <math>\geq 2</math> hours prior to dosing (changed from fast <math>\geq 3</math> hours per Amendment 4)</li> <li>• Added new instructions for patients who cannot comply with the fasting recommendation to:               <ul style="list-style-type: none"> <li>- Ingest only a small amount between 1 hour before to 1 hour after dose <u>and</u></li> <li>- No dairy products 1 hour before after after dose</li> </ul> </li> <li>• Added administration instructions for patients not taking intact capsules, including these lists of acceptable and unacceptable foods and liquids for mixing with Procysbi capsule contents:               <ul style="list-style-type: none"> <li>- Acceptable: applesauce, non-dairy pudding, fruit juice (except grapefruit), Polycitra, Polycitra-K, non-caffeinated soda</li> <li>- Unacceptable: water, milk, dairy products, and other liquids/foods with neutral or basic pH</li> </ul> </li> <li>• Changed instructions to patients taking intact capsules to specify dosing of Procysbi with one of these acceptable foods/liquids (Replaced instruction to take Procysbi with an acidic beverage, as per original protocol through</li> </ul>



		Amendment 4*)
	Modified study visit/assessment schedule	Changed study schedule for newly enrolled patients: <ul style="list-style-type: none"> <li>• Added dose confirmation period on days 1-5</li> <li>• Eliminated Monthly visits, all planned study visits changed to Quarterly</li> </ul>

(Source: Reviewer's own table using information in the RP103-04 Clinical Protocol and Protocol Amendments, versions 1-5; NDA 203389; Module 5.3.5.2)

# Prior to this RP103-04 Protocol Amendment, the Applicant issued an RP103-03 Protocol Amendment, to change patients' initial Procysbi dosing from 70% to 80% of their previous (pre-study) total daily Cystagon dose (RP103-03 Protocol Amendment 4, October 22, 2010). Of the 40 RP103-03 patients who subsequently enrolled in RP103-04, 32 (80%) received a Procysbi starting dose equal to 70% of his/her previous Cystagon dose vs. 8 (20%) patients who received a Procysbi starting dose equal to 80% of the previous Cystagon dose.

\* Previous versions of RP103-04 were consistent with procedures used during RP103-03

† With Amendment 5, RP103-04 enrollment was re-opened to patients who had not previously completed RP103-03

‡ See Figure 36 comparing the PK of opened intact vs. capsules, previously reviewed by Dr. Kristina Estes (see review dated March 30, 2012) are shown in the Appendix, Section 9.4.2 Additional Clinical Pharmacology Information)

#### Amendment 6 (September 26, 2012):

-- Clinical changes:

- Eligibility criteria changed to exclude patients <1 year old
- Maximum study duration increased from 24 to 36 months
- Amended drug administration instructions by making the following changes to the lists of acceptable and unacceptable foods/liquids for Procysbi dosing:
  - Added berry jelly as an acceptable food
  - Specified orange juice as the preferred fruit juice
  - Added alcoholic beverages to the list of unacceptable liquids
- Added optional PK substudy visit for subjects ≤ 6 years old

-- Other changes:

- Revised product description to reflect currently manufactured lots
- Updated the bioanalytical laboratory contact details to reflect that (b) (4) US location receives all PK-PD samples

#### Study Population

All Procysbi clinical trial patients were on treatment with immediate-release cysteamine bitartrate prior to initiation of Procysbi. Until RP103-03 completion/published results, enrollment in RP103-04 was restricted to patients who completed RP103-03. The patients in this study subpopulation, hereafter referred to as "RP103-03 patients", transitioned directly into this extension study. Following the completion of RP103-03 data analysis, enrollment of RP103-04 was re-opened to include patients who did not complete RP103-03 (called "newly enrolled patients"), targeting enrollment to 2 specific patient subgroups of patients were identified for RP103-04 participation: Patients ≤6 years old at the time of enrollment ("patients ≤6 years old") and patients who had previously undergone renal transplantation ("transplant patients").

The following are the key clinical trial eligibility criteria for which were current at the time of patient enrollment:

➤ Key Inclusion Criteria

-- For randomized trial patients:

- Completion of the last visit of Study RP103-03 and willing to continue with RP103

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-- For newly enrolled patients:

- Documented diagnosis of cystinosis
- On a stable dose of Cystagon at least 21 days prior to screening

-- For all patients:

- Within the last 6 months, no clinically significant change from normal in liver function tests [i.e., 1.5 times upper limit of normal (ULN) for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and/or 1.5 times ULN for total bilirubin] and renal function [i.e., estimated glomerular filtration rate (GFR) corrected for body surface area (BSA)] at Screening as determined by the Investigator.
- Subject must have an estimated glomerular filtration rate (GFR) that is >30 mL/minute/1.73 m<sup>2</sup> BSA.
- Sexually active female subjects of childbearing potential (i.e., not surgically sterile [tubal ligation, hysterectomy, or bilateral oophorectomy] or at least 2 years naturally post-menopausal) must agree to utilize the same acceptable form of contraception from Screening through completion of the study.
- Subject must be willing and able to comply with the study restrictions and requirements.
- Subject or their parent or guardian must provide written informed consent and assent (where applicable) prior to participation in the study

➤ Key Exclusion Criteria

-- For randomized trial patients:

- Subjects enrolled in the previous Study RP103-03 who did not complete their last scheduled study visit or did not wish to continue on treatment with RP103.

-- For newly enrolled patients:

- Current history of any of the following conditions or any other health issues that made it, in the opinion of the Investigator, unsafe for them to participate:
  - Inflammatory bowel disease (if currently active) or prior resection of small intestine

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- Heart disease (e.g., myocardial infarction, heart failure, unstable arrhythmias, or poorly controlled hypertension) 90 days prior to Screening
- Active bleeding disorder 90 days prior to Screening
- History of malignant disease within the last 2 years
- Hemoglobin level of <10 g/dL at Screening or, in the opinion of the Investigator, a hemoglobin level that made it unsafe for the subject to participate.
- Known hypersensitivity to cysteamine and penicillamine
- Female subjects who were nursing, planning a pregnancy, known or suspected to be pregnant, or with a positive serum pregnancy screen.
- Subjects who, in the opinion of the Investigator, are not able or willing to comply with the protocol

The protocol listed following reasons for termination of study participation by the Investigator:

- Failure to achieve a meaningful reduction of WBC cystine level—i.e., <1 nmol ½ cystine/mg protein
- Procysbi intolerance
- Change in compliance with inclusion/exclusion criteria(ion) that is/are clinically relevant and affects subject safety,
- Occurrence of AEs that result in the subject or the Investigator requesting study withdrawal, Unacceptable AE(s);
- Occurrence of pregnancy,
- Intake of non-permitted concomitant medication that might affect subject safety or study assessments/objectives, etc.
- Illness that prevented further administration of treatment;
- Changes in the subject's condition that render further treatment unacceptable in the judgment of the Investigator
- Protocol non-compliance

### **Clinical Trial Endpoints**

- Primary endpoints:
  - Safety: assessed by adverse events (AEs), serious adverse events (SAEs), gastric acid reducing medication use, clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, vital signs, and ECGs
  - Steady-state WBC cystine level (nmol ½ cystine/mg protein)
- Other secondary/exploratory endpoints
  - Procysbi dose changes over time and comparison of Procysbi dose with previous Cystagon dose

- Steady-state cysteamine plasma concentration (mg/L)
- Growth (height and weight, with age- and sex-based Z-scores)
- Estimated glomerular filtration rate (GFR)
- Quality of life (tools: PedsQL Version 4.0 Generic core score, SF36 Questionnaire Version 2.0)
- Swallowing difficulty by Visual analog scale (VAS)

### **Study Treatment**

With the exception of the screening period, Procysbi was the only planned cysteamine treatment for patients in RP103-04.

#### ➤ Initial Procysbi dose after switching from Cystagon:

- **RP103-03 patients:** The initial RP103-04 dosage was the same as the last Procysbi dosage administered during the Procysbi arm of RP103-03.

*During RP103-03, Investigators had an opportunity in the middle of the Procysbi treatment arm to increase a patient's Procysbi dose in response to elevated WBC cystine levels. (No dose reductions were permitted during RP103-03.) Doses were increased in 24 of the 40 patients who subsequently enrolled in RP103-04.*

*Initial Procysbi doses in RP103-03 were calculated based on patients' previous daily Cystagon doses. For the 32/40 patients who were enrolled using the original RP103-03 dosing procedures, the initial daily Procysbi dose was equal to 70% of their previous Cystagon dose. The remaining 8 patients were enrolled after protocol amendments—procedures specified either 80 or 90% of their previous daily Cystagon dose.*

*For 27/32 patients enrolled under the original protocol and 3/8 patients enrolled after the dosing-related protocol amendments, doses were increased during RP103-03 and these adjusted doses were carried over into RP103-04.*

- **Newly enrolled patients:** The initial RP103-04 total daily dose was equal to 70% of the previous total daily Cystagon dose, given in 2 divided daily doses at 12-hour intervals.

#### ➤ Study drug administration procedures

- Administration of intact Procysbi capsules
  - From RP103-03 until RP103-04 Amendment 5: instructed to take Procysbi with an acidic beverage
  - After Amendment 5 of RP103-04: instructed to take Procysbi with an acceptable food/beverage (see below)
- Administration of Procysbi for patients unable/unwilling to take intact capsules (initiated after Amendment 5, allowed administration of open Procysbi capsule via mixtures of Procysbi capsule contents and specified food/liquid within 2 hours of preparation; the

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mixture must be refrigerated between preparation and administration

- Dosing in food: open all capsules for the dose and sprinkle contents onto approximately 4 ounces of an acceptable soft food (see below). Gently stir the medication beads into the soft food, and eat the entire amount of food. This may be followed by 8 ounces (1 cup) of an acceptable liquid
- Dosing in liquid: open all the capsules for the dose and sprinkle the contents into 4-6 ounces of an acceptable liquid. Mix/shake gently for 5 minutes, then:
  - Syringe administration: aspirate the RP103-liquid mixture into a dosing syringe. Administer the entire dose via gastrostomy tube
  - Administration by mouth: Drink all of the RP103-liquid mixture.
- Acceptable liquids/foods for Procysbi dosing: orange juice (preferred) or other fruit juice (except grapefruit), applesauce, non-dairy pudding, Polycitra, Polycitra-K, non-caffeinated soda, berry jelly  
(Unacceptable foods and liquids: water milk, dairy products, alcoholic beverages, other liquids/foods with neutral or basic pH)
- Timing of Procysbi doses with respect to meals/snacks, depending on protocol amendment
  - RP103-03 (all) through Amendment 3 of RP103-04
    - Eat immediately prior to Procysbi dose
    - Withhold dairy products for 1 hour before and 1 hour after dosing
  - Amendment 4 of RP103-04
    - Fast  $\geq 3$  hours prior to dosing; and
    - Ingest meal between 30 & 60 minutes after dose (withhold dairy products for 1 hour after dose)
  - Amendment 5 of RP103-04 until data cutoff
    - Recommended fast  $\geq 2$  hours prior to dosing
    - Wait at least 30 minutes after dose before eating
    - For patients who cannot comply with the general fasting recommendations, ingest only a small amount between 1 hour before and 1 hour after dose and withhold dairy products during this time
- Dosage adjustments: The Investigator was permitted to make Procysbi dosage adjustments in response to safety information (i.e., symptoms of medication intolerance) or PD data (i.e., WBC cystine levels  $>1$  nmol  $\frac{1}{2}$  cystine/mg protein) obtained at each study visit.
- Medication diary:
  - A daily diary was dispensed to each patient/family to keep a record of (1) Procysbi doses, administration times, administration procedures (i.e.,

fasting/timing of meals with respect to doses, liquid or food taken with Procysbi), and (2) gastric acid reducing (GAR) drugs (prescription and over the counter).

- At each study visit, diaries were reviewed for completeness and collected by study personnel, and a new diary was dispensed.
- Continued non-compliance with diary completion was specified by the Applicant as a reason for early study termination.

Note: Due to Procysbi re-supply issues in December 2010 and January 2011, 7 patients were treated with Cystagon during  $\geq 1$  period of Procysbi unavailability (maximum reported duration 18 days).

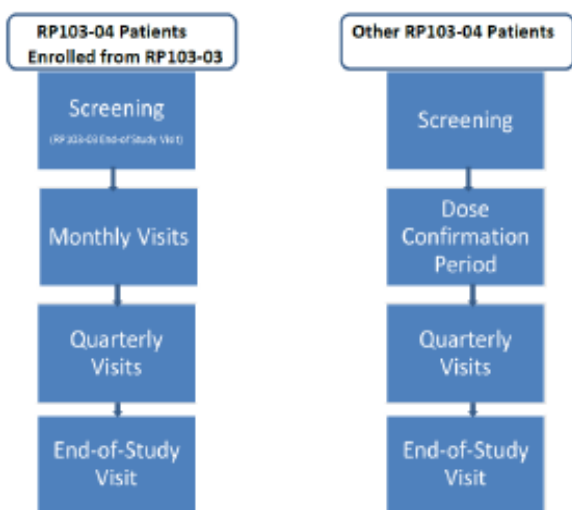
### **Prior and Concomitant Medications**

- Procysbi was the only cysteamine formulation permitted in RP103-04.\*
- Subjects were asked to stop gastric acid reducing (GAR) medications at least 12 hours before receiving their first dose of RP103 until study termination. However, GAR medications were allowed in cases of intolerable gastric upset, at the discretion of the Investigator. Use of GAR drugs was evaluated as a clinical trial safety outcome.
- Illegal drug use and alcohol use were prohibited during the study.
- There were no restrictions on the use of other concomitant medications during the trial.

### **Study Procedures:**

- Study Visits: scheduled study assessments and visits differed according to patient enrollment group (shown in Figure 5).

**Figure 5: RP103-04 Study Visit Schematic- Comparison of RP103-03 and Newly Enrolled Patients**



(Source: Clinical Review by Dr. Carla Epops dated April 26, 2013; Figure 8 entitled "RP103-04 Study Trial Schematic", page 63/112)

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- Screening:
  - For RP103-03 patients, screening was performed concurrently with the RP103-03 End-of-Study visit
  - For newly enrolled patients, up to 28 days prior to Study Day 1
- Dose confirmation period (*newly enrolled patients only*): Study Days 1-5
  - Day 1 (while still on Cystagon): morning study visit with PK/PD measurements drawn 5.75 hours after last Cystagon dose
  - First Procysbi dose administered in clinic
  - Days 4 and 5: Study visits with PK/PD measurements 30 minutes post- Procysbi dose
    - PK blood sample (plasma cysteamine level) 0.5 hour (30 minute) post- Procysbi dose; PD sample (WBC cystine level)
    - Procysbi dose adjustment based on WBC cystine level, if needed
- Planned study visits with PK/PD assessments: For RP103-03 patients, frequency of planned study visits/assessments was monthly (minimum of 6 consecutive visits), followed by Quarterly Study visits/assessments for the remainder of study participation. Only Quarterly Study visits/assessments were planned for newly enrolled patients, all of whom were enrolled after elimination of Monthly Study visits by Amendment 5.

*Quarterly Study Visits were planned for the 15<sup>th</sup> day ( $\pm 7$  days) of the first month of each calendar quarter (i.e., January 15, April 15, July 15 and October 15).*
- End-of-Study Visit: within 7 ( $\pm 2$  days) from the last completed study visit or from the date of decision to terminate study participation

➤ Study Assessments

**Table 8: RP103-04 Schedule of Assessments**

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

(Source: Adapted from Applicant's Table 2, entitled "Schedule of Events"; Interim Clinical Study Report, pages 44-49, Module 5.3.5.2)

\* Dose confirmation period is only applicable to newly enrolled patients

# Newly enrolled patients did not have any Monthly Study visits

**Planned Methods of Analysis**

Because RP103-04 is an ongoing trial, the database remains unlocked. The Applicant submitted an interim clinical study report and analyses to support these application (b) (4) RP103-04 is a single-arm clinical trial intended to perform longitudinal analyses. Summary statistics were provided for outcome variables (and change from baseline) over time (N, mean, median, SD, minimum, and maximum). Missing data were not imputed.

Two study populations were planned for analysis:

- PK/PD population: Patients with  $\geq 1$  PK/PD measurement (n=59)
- Safety population: Patients who received  $\geq 1$  of the study drug (n=59)

Analyses of efficacy outcome variables are reported for the PK/PD population, and for each of the 3 study sub-populations (RP103-03 patients, patients  $\leq 6$  years old, and transplant patients). However, this trial was uncontrolled and not powered to provide substantial evidence of efficacy. Therefore, only descriptive statistics are presented for inter-group comparisons. Formal dose-response and exposure response analyses to support extrapolation of efficacy were performed by the pharmacometrics review team (see Clinical Pharmacology review dated June 29, 2015).

For the transplant patients, discussions of subgroup analyses are limited due to the very small



population size and large baseline inter-patient variability, which interfere with data interpretation.

For safety analyses, no formal hypothesis-testing analysis of adverse event (AE) rates was planned. Planned AE tabulations included the following:

- By-subject listings planned for the following: treatment-emergent AEs, subject deaths; SAEs; and AEs leading to withdrawal
- Summarization of adverse events in tables by frequency/incidence rates—for events that were considered treatment-emergent, defined as any AE that emerged during treatment in study RP103-04, having been absent pretreatment, or worsened relative to the pretreatment state
- Coding of adverse events by the MedDRA (version 12.1) Preferred Term and System/Organ/Class (SOC)
- Presentation of treatment-emergent adverse event (TEAE) coded by study drug causality—i.e., definitely, probably, and possibly related AEs

For laboratory values, the actual value and change from baseline was summarized for each clinical laboratory assessment. In the event of repeat values, the last non-missing value per visit, per time point was used. Vital sign measurements and physical examination findings, and ECG data were presented as by-subject listings.

## 6 Review of Efficacy

### Efficacy Summary

To demonstrate the efficacy of Procysbi in patients  $\leq 6$  years old with nephropathic cystinosis, the Applicant submitted data from 13 patients enrolled in a single-arm, open label clinical trial (RP103-04), which is not powered to provide substantial evidence of efficacy. However, because the course of the disease and expected effects treatment response are sufficiently similar for all patients nephropathic cystinosis, regardless of age, under the Code of Federal Regulations [21 CFR 314.55(a) and 21 CFR 601.27 (a)], the efficacy of Procysbi can be extrapolated from adequate and well-controlled studies in older patients. Procysbi was approved for patients  $\geq 6$  years old under the 505(b)(2) regulatory pathway, based on the demonstration of noninferiority to immediate-release cysteamine bitartrate (Cystagon), its listed drug, in a 9-week randomized, cross-over trial (RP103-03). Efficacy was assessed using measurements of white blood cell (WBC) cystine, a pharmacodynamic biomarker of intracellular cystine accumulation which is used in clinical practice to evaluate treatment response, along with reliance on the FDA's prior finding of effectiveness for Cystagon.

In RP103-04, WBC cystine level was also specified as the primary efficacy endpoint. Compared to patients  $> 6$  years old, WBC cystine levels were higher in the patients  $\leq 6$  years old. The mean ( $\pm$ SD) WBC cystine level at each study visit ranged from 0.86 ( $\pm 0.51$ ) to 2.00 ( $\pm 1.73$ ) nmol  $\frac{1}{2}$

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cystine/mg protein for patients  $\leq 6$  years old (based on Study Visits for which there are data for  $>60\%$  of patients), compared to  $0.41 (\pm 0.39)$  to  $0.56 (\pm 0.44)$  nmol  $\frac{1}{2}$  cystine/mg protein for the patients  $>6$  years old (i.e., RP103-03 patients). While the patients with  $>6$  years old had mean WBC cystine levels  $<1$  nmol  $\frac{1}{2}$  cystine/mg protein, the usual therapeutic target, at all RP103-04 Study Visits, mean levels for the patients  $\leq 6$  years old were less than  $<1$  nmol  $\frac{1}{2}$  cystine/mg protein at 2 of the 5 analysis Study Visits completed by  $>60\%$  of patients. However, the newly enrolled patients  $\leq 6$  years old were not required to have the same baseline disease control as patients  $>6$  years old who completed RP103-03, and therefore baseline WBC cystine levels were higher in the patients  $\leq 6$  years old.

At baseline, 5 of the 13 (38%) patients  $\leq 6$  years old had WBC cystine levels  $<1$  nmol  $\frac{1}{2}$  cystine/mg protein [Mean ( $\pm$ SD)  $1.41 (\pm 1.03)$  nmol  $\frac{1}{2}$  cystine/mg protein]. For the 12 patients who had an available assessment after 12 months of Procysbi treatment, mean ( $\pm$ SD) baseline WBC cystine level was  $1.40 (\pm 1.08)$  nmol  $\frac{1}{2}$  cystine/mg protein. After 12 months of treatment, mean ( $\pm$ SD) WBC cystine level was  $1.13 (\pm 0.56)$  nmol  $\frac{1}{2}$  cystine/mg protein. For the patients with WBC cystine level  $<1$  nmol  $\frac{1}{2}$  cystine/mg protein at this study time point, mean ( $\pm$ SD) daily Procysbi dose was  $1062 (\pm 332)$  grams/ $m^2$ /day.

As of data cutoff, 11 patients (85%) achieved at least 1 WBC cystine levels  $<1$  nmol  $\frac{1}{2}$  cystine/mg protein, including 6 of the 8 patients with WBC cystine level  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein. For these 6 patients with poor baseline disease control who achieved desirable WBC cystine levels, their mean ( $\pm$ SD) Procysbi daily dose increased from  $856 (\pm 315)$  mg/ $m^2$ /day (median 749 mg/ $m^2$ /day) to  $1172 (\pm 268)$  mg/ $m^2$ /day (median 1138 mg/ $m^2$ /day) at patients' last visit prior to data cutoff. Based on these data, differences in WBC cystine level between patient subgroups appear to be due to differences in baseline disease control and suboptimal cysteamine dosing, rather than differences in underlying disease characteristics. Thus, these data provide supportive evidence of Procysbi's efficacy in patients  $\leq 6$  years old to strengthen extrapolation conclusions.

To fulfill the pre-requisites for extrapolation of efficacy, RP103-04 data were used to perform exposure-response and dose-response analyses. Comparisons between newly enrolled patients  $\leq 6$  years and patients  $>6$  years old previously enrolled in RP103-03 revealed similar relationships for both exposure-response and dose-exposure for the 2 patient subgroups. Therefore, this reviewer concludes that sufficient evidence of Procysbi efficacy exists to support approval in patients ages 2 to 6 years old.

### 6.1 Indication

The efficacy supplement under review was submitted by the Applicant to support a proposal to expand the current Procysbi indication, management of nephropathic cystinosis in patients ages 6 years and older, to include patients as young as 2 years of age. In the submission, the Applicant also included a proposal to (b) (4)

(b) (4)

(b) (4)

### 6.1.1 Methods

The efficacy of Procysbi for the treatment of nephropathic cystinosis in patients age 2 to 6 years old was extrapolated from efficacy data in older patients, with supportive data from patients enrolled in an open-label, single arm clinical trial (RP103-04) aimed to evaluate long-term Procysbi treatment patients in nephropathic cystinosis. For older patients, the efficacy of Procysbi was established using data from a 9-week, randomized, open-label cross-over clinical trial (RP103-03), which demonstrated non-inferiority of Procysbi to the FDA approved immediate-release formulation of cysteamine bitartrate (Cystagon, NDA 020392, approved August 15, 1994). Based on these data, the FDA concluded that the Applicant provided sufficient evidence of a comparable effect on the pharmacodynamic biomarker of white blood cell (WBC) cystine concentration for/to support approval under the 505(b)(2) regulatory pathway. (The reader is referred to the Clinical Review by Dr. Carla Epps dated April 26, 2013.) As a 505(b)(2) new drug application (NDA), the FDA's findings of safety and efficacy relied on data from clinical trials with immediate-release cysteamine and clinical experience of Cystagon for treatment of nephropathic cystinosis, along with appropriate bridging clinical pharmacology studies. (The reader is referred to the Clinical Pharmacology review of the original NDA by Dr. Kristina Estes dated March 30, 2012.)

The Applicant submitted interim analyses of Study RP103-04 data (cutoff date July 10, 2013). These data were obtained from patients continuing Procysbi treatment following completion of Study RP103-03 (n=40, referred to as "RP103-03 patients" in this review), as well as 19 newly enrolled, Cystagon-treated patients from two patient populations not previously represented in Procysbi clinical trials, patients age 2 to 6 years old (n=13, referred to as "≤6 years old" in this review) and patients who had previously undergone renal transplantation for end-stage renal disease due to nephropathic cystinosis (n=6, referred to as "transplant patients" in this review). At the time of data cutoff, mean (±SD) Procysbi treatment duration in RP103-04 was 26.8 (±6.5) months for the RP103-03 patients and 17.2 (±1.9) months for the patients ≤6 years old.

The efficacy evaluation for this review focused on:

1. Evidence to support the extrapolation of the efficacy in patients aged 2 to 6 years old from Procysbi clinical trial data in older patients (for Supplement 10)
2. Evaluation of dose-response, in combination with clinical pharmacology data of exposure-response to inform dosing for patients age 2 to 6 years old (for Supplement 10)
3. Review of extension trial data in patients who completed RP103-03, (b) (4)

(b) (4)

to demonstrate comparability/similarity in exposure-response and dose-response between the patients  $\leq 6$  years old and the RP103-03 patients to support the use of extrapolation for Supplement 10 and inform dosing in patients age 2 to 6 years of age.

The reader is referred to Sections 5.3 (Discussion of Individual Studies/Clinical Trials) for details of the RP103-04 clinical trial design. As stated in Section 5, although 14 patients were enrolled in the  $\leq 6$  year old patient subgroup, one patient did not receive any doses of Procysbi; therefore, this patient was excluded from both the safety and PK/PD analysis datasets.

Efficacy subset analyses were performed using patient subgroups defined based on the following characteristics:

1. RP103-03 patients, consisting of 40 of the 41 patients previously enrolled in RP103-03. *Of note, the efficacy analyses for RP103-03 were conducted using a "Per Protocol" dataset consisting of 39 of the 41 patients who completed the trial. 38 of these 39 patients enrolled in RP103-04. Two patients who completed RP103-03 were excluded from RP103-03 efficacy analyses due to elevated WBC cystine levels ( $> 2 \text{ nmol } \frac{1}{2}$  cystine/mg protein). Both of these patients subsequently enrolled in RP103-04.*
2. The group enrolled in RP103-04 consists of 38 of the 39 Per Protocol patients and the 2 patients excluded from this dataset.
3. Patients  $\leq 6$  years old (n=13)
4. Transplant patients (n=6)

For some descriptions and analyses included in this review, a "newly enrolled" patient subgroup (n=19), which combines the  $\leq 6$  years old and transplant patient subgroups, has also been used.

#### Limitations of RP103-04 Clinical Trial Data

In order to interpret RP103-04 clinical trial data, the following factors need to be considered:

- Change in eligibility criteria which eliminated the requirement that patients must be on a suitable dose of cysteamine that produces a meaningful reduction in WBC cystine levels, leading to differences in baseline disease control between patient subgroups
- The lack of standardized dosing leading to substantial inter-patient variability in Procysbi dose
- The intra-patient variability in dose due to dosage adjustments during study participation
- Interval between enrollment of RP103-03 patients and newly enrolled patients and decreased assessment frequency for newly enrolled patients, providing notably fewer opportunities for dose optimization and leading to disproportionate

In addition, because Study Visits were named according to the visit schedule (e.g., Monthly 1, Quarterly 1, etc.), Study Visit names referred to different study time points for RP103-03 patients and newly enrolled patients, which precluded performing inter-group analyses by Study Visit. Therefore, this reviewer recoded Study Visit names for the newly enrolled patients to be consistent with the RP103-03 patients' Study Visits. For the purposes of clarification and consistency, only these recoded study visit names are used in this review and are referred to as "Adjusted Study Visits". In Table 9, Adjusted Study Visits are shown along with the corresponding Study Visit names assigned by the Applicant for both the RP103-03 and newly enrolled patients.

**Table 9: Reviewer's Renaming of Study Visits to "Adjusted Study Visits" (in Order for Study Visit Names to Represent Consistent Study Time Points for Newly Enrolled and RP103-03 Patients)**

Original Study Visit Name		Adjusted Study Visit Name
RP103-03 Patients	Newly Enrolled Patients	
Monthly 1	----*	Monthly 1*
Monthly 2	----*	Monthly 2*
Monthly 3	Quarterly 1	Monthly 3
Monthly 4	----*	Monthly 4*
Monthly 5	----*	Monthly 5*
Monthly 6	Quarterly 2	Monthly 6
Quarterly 1	Quarterly 3	Quarterly 1 (Q1)
Quarterly 2	Quarterly 4	Quarterly 2 (Q2)
Quarterly 3	Quarterly 5	Quarterly 3 (Q3)
Quarterly 4	Quarterly 6	Quarterly 4 (Q4)

\* Indicates Study Visit for RP103-03 patients only.

Transplant patients: Subgroup analyses are generally not discussed in detail. This subgroup had a very small population size which consisted of 5 patients at most study time points. (Following the dose-finding period, one transplant patient was discovered to be noncompliant with treatment and was withdrawn from study participation by the Investigator.) Because there was substantial inter-patient variability in baseline disease control and cysteamine bitartrate doses, interpretations of efficacy analyses in this patient population are not informative.

### 6.1.2 Demographics

All patients enrolled in RP103-04 were previously treated with Cystagon. In other words, no cysteamine-naïve patients were enrolled in RP103-04 or the previous randomized cross-over clinical trial, RP103-03. The duration of patients' prior Cystagon treatment or date of nephropathic cystinosis diagnosis was not provided. However, medical history information suggests patients' duration of immediate-release cysteamine treatment prior to enrollment in Procysbi clinical trials was highly variable.

Baseline patient data for all RP103-04 patients included the PK/PD and safety datasets (N=59) are summarized in Tables 10 and 11 —demographic data are shown in Table 10, and baseline clinical data are shown in Table 11. For all parameters, descriptive data analyses are presented for the entire dataset and for each of the 3 patient subgroups; i.e., “RP103-03” patients (patients who completed RP103-03 prior to enrollment), patients “≤6 Years Old” (age ≤6 years at the time of enrollment in RP103-04), and “transplant” patients (patients who previously received a renal transplant).

All baseline dosage and WBC cystine levels represent levels at the time of enrollment in RP103-04. Therefore, for the RP103-03 patients, “initial” Procysbi doses represent the last prescribed Procysbi dosage from RP103-03, and baseline WBC cystine measurements were obtained on this initial Procysbi dosage.

**Table 10: Demographics for the RP103-04 PK/PD Patient Population**

Parameter	RP103-04 PATIENT GROUP*			
	All Patients N=59	RP103-03 n=40	Newly Enrolled	
			≤6 Years Old n=13	Transplant n=6
Age (years)				
n	59	40	13	6
Mean (±SD)	10.9 (±6.0)	11.5 (±3.6)	4.0 (±1.6)	21.7 (±7.2)
Median	10	11	5	20.5
Range	2 – 32	7 – 20	2 – 6	13 – 32
Gender (n, (%))				
Male	37 (62.7)	23 (57.5)	10 (76.9)	4 (66.7)
Female	22 (37.3)	17 (42.5)	3 (23.1)	2 (33.3)
Race (n, (%))				
White	58 (98.3)	39 (97.5)	13 (100.0)	6 (100.0)
Other	1 (1.7)	1 (2.5)	0 (0.0)	0 (0.0)
Ethnicity (n, (%))				
Hispanic/Latino	3 (5.1)	2 (5.0)	1 (7.7)	0 (0.0)
Non-Hispanic/Latino	56 (94.9)	38 (95.0)	12 (92.3)	6 (100.0)
Country (n, (%))				
USA	33 (55.9)	23 (57.5)	7 (53.8)	3 (50.0)
France	22 (37.3)	13 (32.5)	6 (46.2)	3 (50.0)
Netherlands	4 (6.8)	4 (10.0)	0 (0.0)	0 (0.0)
Height Z-score				
n	54*	38*	13	2*
Mean (±SD)	-1.35 (±1.03)	-1.27 (±0.93)	-1.56 (±1.38)	-1.66 (±0.24)
Median	-1.48	-1.27	-1.65	-1.66
Range	(-4.06 to +1.08)	(-3.09 to +0.42)	(-4.06 to +1.08)	(-1.83 to -1.49)
Estimated GFR				
n	59	40 <sup>†</sup>	13	6
Mean (±SD)	68.5 (±26.2)	66.0 (±26.3)	76.2 (±28.5)	67.3 (±20.0)
Median	66.0	60.2	78.8	70.7
Range	(25.8 – 117.4)	(25.8 – 116.7)	(30.1 – 117.4)	(34.0 – 87.2)

(Source: Clinical Reviewer’s table using Applicant’s Analysis Data in NDA 203389; Module 5.3.5.2)

\* Height Z-scores were not included for adult patients (1 RP103-03 patient and 4 transplant patients)

See footnotes to Table 11

† For 1 patient in the RP103-03 subgroup, baseline eGFR/creatinine was missing. The first available creatinine measurement was used for interpolation and to derive baseline eGFR. This measurement was similar to the last measurement obtained in RP103-03.

**Table 11: Baseline Medication Doses and WBC Cystine Levels**

Parameter	PATIENT GROUP			
	All N=59	RP103-03 n=40	Newly Enrolled	
			≤ 6 Years Old n=13	Transplant n=6
<b>Previous Cystagon dose (mg/m<sup>2</sup>/day)</b>				
n	59	40	13	6
Mean (±SD)	1391 (±388)	1537 (±320)	1099 (±362)	1048 (±317)
Median	1370	1515	984	1093
Range	629 – 2198	795 – 2198	741 – 2115	629 – 1421
<b>Initial RP103-04 Procybsi dose</b>				
<b>Total daily dose (mg/m<sup>2</sup>/day)</b>				
n	59	40	13	6
Mean (±SD)	1133 (±322)	1277 (±246)	814 (±251)	863 (±245)
Median	1169	1256	761	899
Range	526 – 1923	695 – 1923	526 – 1474	545 – 1154
<b>% Previous Cystagon dose</b>				
n	59	40	13	6
Mean (±SD)	82.3 (±16.1)	83.7 (±7.9)	74.6 (±2.0)	89.4 (±46.2)
Median	86.1	86.5	73.5	79.9
Range	65.6 – 183.3	68.8 – 105.0	66.7 – 87.5	65.6 – 183.3
<b>Baseline WBC Cystine (nmol ½ cystine/mg protein)</b>				
<b>Actual WBC Cystine level</b>				
n	59	40	13	6
Mean (±SD)	1.05 (±1.60)	0.79 (±1.68)	1.41 (±1.03)	2.05 (±1.73)
Median	0.52	0.35	1.19	1.46
Range	0.03 – 10.60**	0.03 – 10.6**	0.12 – 3.33	0.33 – 4.34
<b>WBC Cystine Level Group</b>				
<1	41 (69.5)	34 (85.0)	5 (38.5)	2 (33.3)
≥1 to ≤2	11 (18.6)	4 (10.0)	5 (38.5)	2 (33.3)
>2	7 (11.9)	2 (5.0)	3 (23.1)	2 (33.3)

(Source: Clinical Reviewer's table using Applicant's Analysis Data in NDA 203389; Module 5.3.5.2)

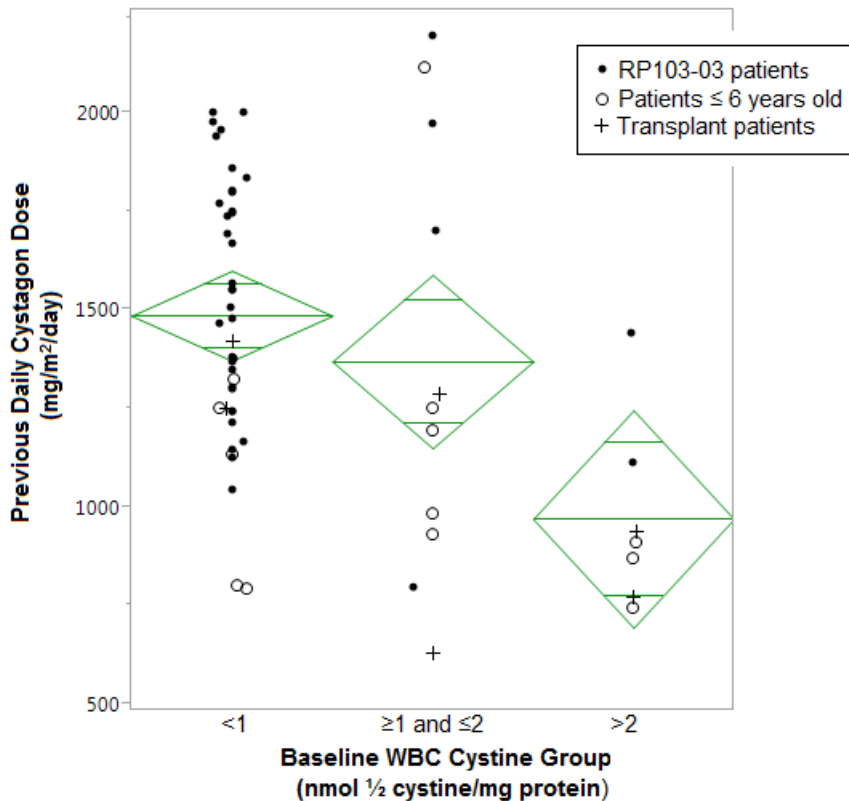
\* RP103-04 Patient Group definitions:

- RP103-03: patients who completed RP103-03 prior to enrollment in RP103-04
- Newly enrolled: patients enrolled directly in RP103-04 without prior Procybsi treatment
- ≤ 6 Years Old: newly enrolled patients ages 2 to 6 years at the time of enrollment in RP103-04
- Transplant- newly enrolled patients with history of renal transplant

\*\* Baseline WBC cystine level for Subject 03009 was 10.6 nmol ½ cystine/mg protein; the Applicant reported that the patient was known to be noncompliant with Cystagon treatment during the last period of RP103-03.

Because enrollment criteria differed for the newly enrolled patients and RP103-03 patients WBC cystine levels were higher for the newly enrolled patients, compared to the RP103-03 patients. Newly enrolled patients were also receiving lower doses of Cystagon (corrected for body surface area) prior to enrollment. The relationship between baseline WBC cystine level and previous Cystagon total daily dose is shown in Figure 6. Patients with desirable baseline WBC cystine levels were receiving higher mean Cystagon doses prior to enrollment.

**Figure 6: Comparison of Previous Cystagon Daily Doses for Baseline WBC Cystine Groups**



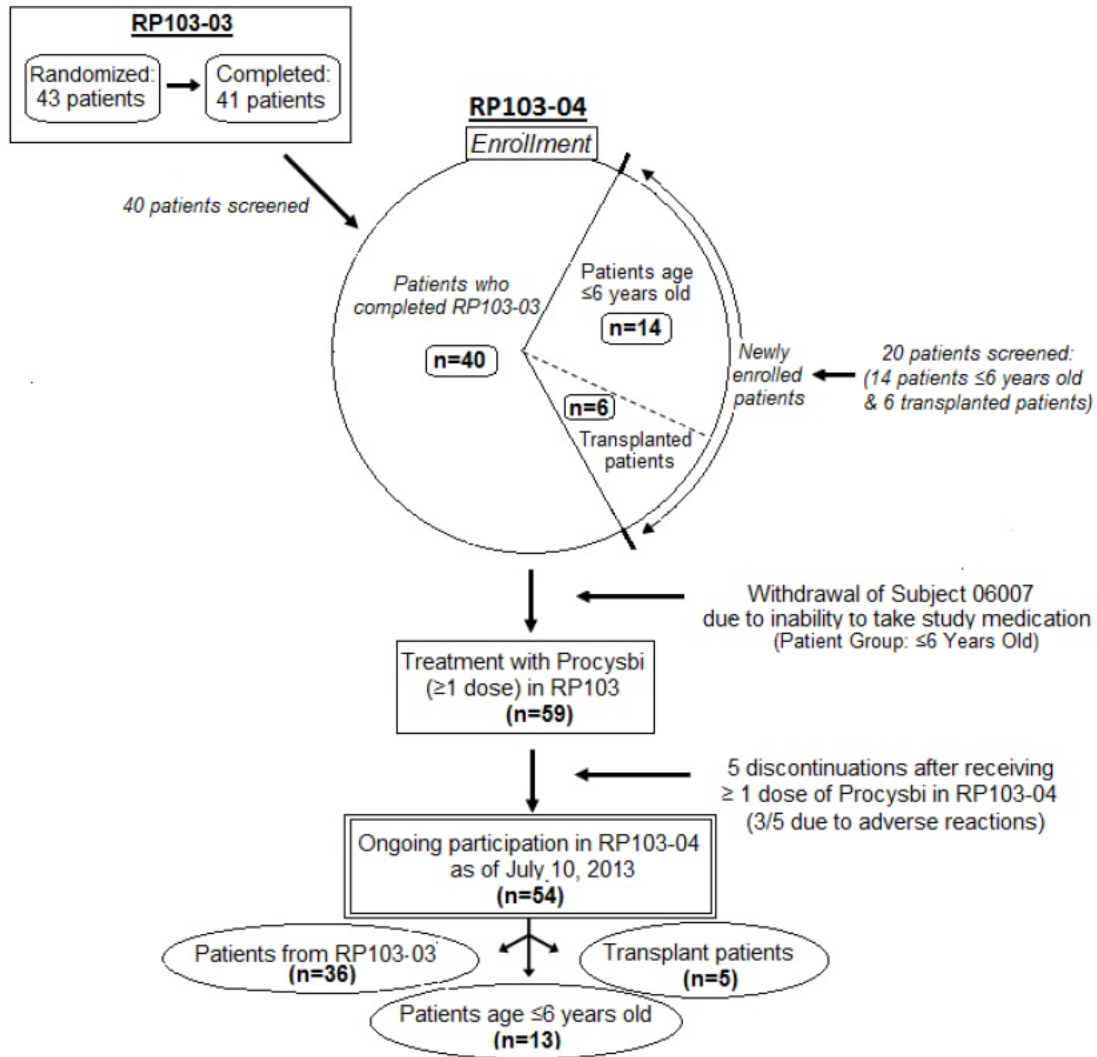
(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

### 6.1.3 Subject Disposition

Patient enrollment and disposition at data cutoff (July 10, 2013) are summarized in Figure 7 and Table 12.



**Figure 7: Subject Disposition as of Data Cut-off Date (July 10, 2013)**



(Source: Reviewer's own figure adapted from information provided in the Interim Clinical Study Report; NDA 203389; Module 5.3.5.2)

**Table 12: RP103-04 Patient Disposition Summary**

Patient Status	n
Number Screened	60
Number Enrolled	60
PK/PD Population	59
Safety Population	59
Discontinuations:	5
No doses of Procysbi administered*	
• Patients ≤6 years old	1
After initiation of Procysbi**	
• RP103-03 patients	4
• Patients ≤6 years old	0
• Transplant patients	1

(Source: Clinical Reviewer's figure using Applicant's Analysis Data in NDA 203389; Module 5.3.5.2)

Reason for discontinuation:

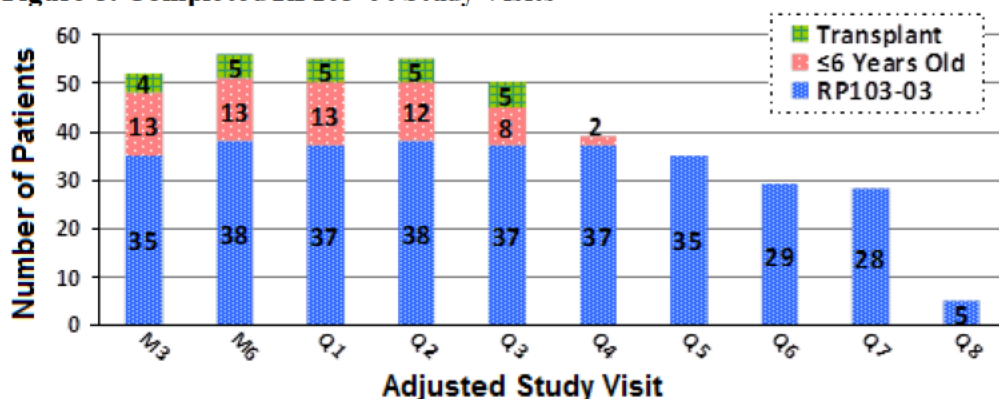
\*Patient unable to take study medication

\*\*RP103-03 patients: 3 adverse reactions, 1 withdrawal of consent

Transplant patient: 1 physician judgment

At the time of data cutoff, the mean ( $\pm$ SD) duration of Procysbi treatment was 26.8 ( $\pm$ 6.5) months for the RP103-03 patients vs. 17.2 ( $\pm$ 1.9) months for the patients  $\leq$ 6 years old. The number of completed Study Visits (by Adjusted Study Visit name) is shown in Figure 8 for each of the patient subgroups.

**Figure 8: Completed RP103-04 Study Visits**



(Source: Clinical Reviewer's figure using Applicant data in NDA 203389; Module 5.3.5.2)

#### 6.1.4 Analysis of Primary Endpoint(s)

The pre-specified primary efficacy endpoint for RP103-04 (also used as the primary endpoint for RP103-03), is WBC cystine level, an established pharmacodynamic (PD) marker of intracellular cystine depletion that has been shown to correlate with long-term, meaningful clinical outcomes in patients with nephropathic cystinosis.[21,24] In clinical practice, WBC cystine levels are used

## Clinical Review

Lauren Weintraub, MD

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Procysbi (delayed-release cysteamine bitartrate capsules)

to monitor disease and guide cysteamine dose adjustment to achieve a desirable clinical response, which consensus treatment guidelines define as WBC cystine levels below the upper limit for heterozygous carriers who are asymptomatic ( $<1$  nmol  $\frac{1}{2}$  cystine/mg protein using current standard laboratory methodology).[11] Reference WBC cystine ranges and therapeutic target levels are the same for all patients with nephropathic cystinosis, regardless of age.[12]

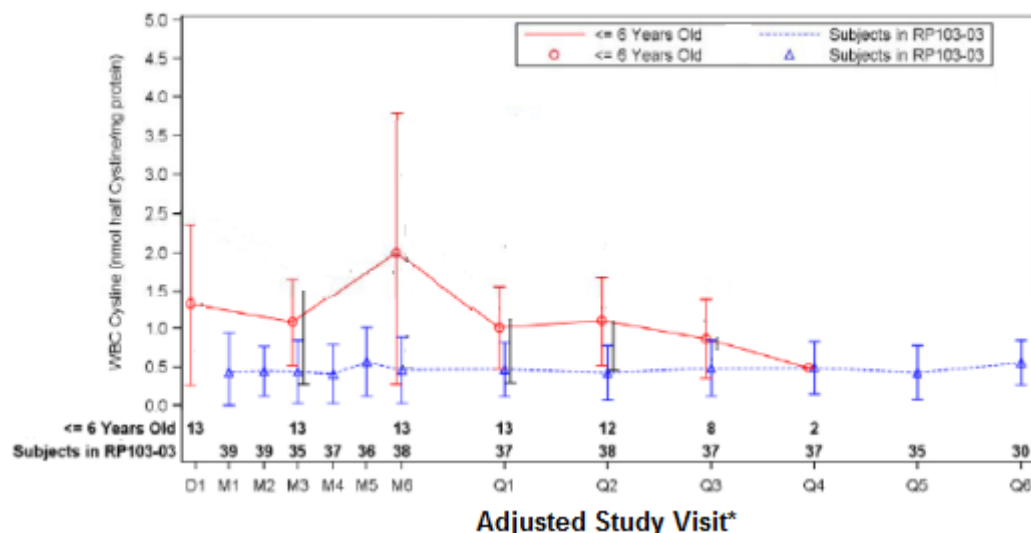
In patients older than 6 years of age, from whom the efficacy of Procysbi is being extrapolated for patients age 2 to 6 years old, mean  $\pm$ SD WBC cystine levels during the Procysbi treatment arm of Study RP103-03 ( $0.52 \pm 0.06$  nmol  $\frac{1}{2}$  cystine/mg protein) were comparable to levels during the Cystagon treatment arm ( $0.44 \pm 0.06$  nmol  $\frac{1}{2}$  cystine/mg protein; difference  $0.08 \pm 0.03$ , non-inferiority margin  $< 0.3$ , 95.8% confidence interval 0.01 to 0.15, p-value  $< 0.0001$ ). This 9-week cross-over trial was used to support NDA approval under the 505(b)(2) regulatory pathway with Cystagon as the listed drug. (The reader is referred to the clinical review by Dr. Carla Epps dated April 26, 2013.)

For 40 of the 41 patients older than 6 years old who completed RP103-03, serial WBC cystine measurements on Procysbi treatment for up to 34 months duration are available from the Interim RP103-04 data analyses. A total of 504 measurements were available for this patient subgroup, with the last assessments for the 36 patients still enrolled at the time of data cutoff obtained at time points ranging from Study Month 22 to 31.

At all analysis time points during RP103-04, mean WBC cystine levels for the RP103-03 patients were  $< 1$  nmol  $\frac{1}{2}$  cystine/mg protein. Tables with WBC cystine level summary for the RP103-03 patients can be found in the Appendix, 9.4.3 Additional Efficacy Tables/Figures). Thus, it appears that long-term Procysbi treatment can maintain WBC cystine levels in the therapeutic target range.

For the 13 patients  $\leq 6$  years old, 61 WBC cystine measurements were available in the submitted interim RP103-04 data. Mean WBC cystine levels in patients  $\leq 6$  years old were greater than 1 nmol  $\frac{1}{2}$  cystine/mg protein at 5 of the 6 analysis time points for which  $> 50\%$  of patients had available data. Thus, patients  $\leq 6$  years old had higher mean WBC cystine levels than the RP103-03 patients (Figure 10 and Table 9).

**Figure 9: Mean ( $\pm$ SD) WBC Cystine Levels ( $\text{nmol } \frac{1}{2}$  cystine/mg protein) by Patient Group**



(Source: Adapted from Applicant's Figure 2 entitled "Mean ( $\pm$ SD) WBC Cystine Level ( $\text{nmol } \frac{1}{2}$  cystine/mg protein) vs. Time at "Collected Visits" (Collected Visits)"; Interim Clinical Study Report page 82/201; Module 5.3.5.2)  
 Abbreviations: M, monthly visit; Q, quarterly visit

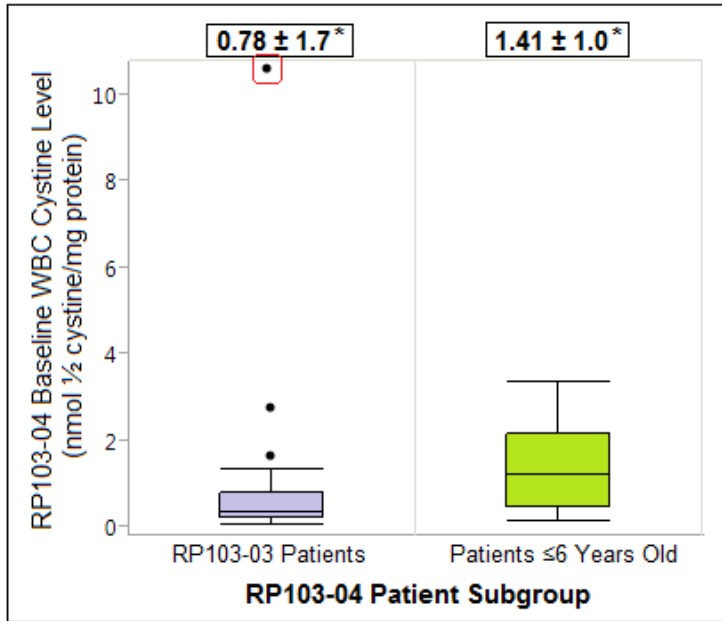
Study visit name is defined by study visit schedule for RP103-03 patients, who had least 6 monthly study visits, followed by quarterly study visits

For newly enrolled patients, who had only quarterly visits, M3=1<sup>st</sup> quarterly visit, M6=2<sup>nd</sup> quarterly visit, Q1=3<sup>rd</sup> quarterly visit, etc.

However, baseline WBC cystine levels (i.e., last WBC cystine level obtained prior administration of the first Procysbi dose in RP103-04) were higher for the patients  $\leq 6$  years old than RP103-03 patients (Figure 10). Baseline values for 8 of the 13 (62%) patients  $\leq 6$  years were  $\geq 1$   $\text{nmol } \frac{1}{2}$  cystine/mg protein vs. 6 of the 40 RP103-03 patients (15%). Median baseline levels were 1.19 and 0.36 for the patients  $\leq 6$  years old and RP103-03 patients, respectively. (Mean values are shown in Figure 10.)

Unlike the RP103-03 patients, patients  $\leq 6$  years old were not required to be on a stable dose of Cystagon which achieved a desirable WBC cystine concentration prior to clinical trial participation. Therefore baseline WBC cystine levels were notably higher among the patients  $\leq 6$  years old (Figure 10 and Figure 11).

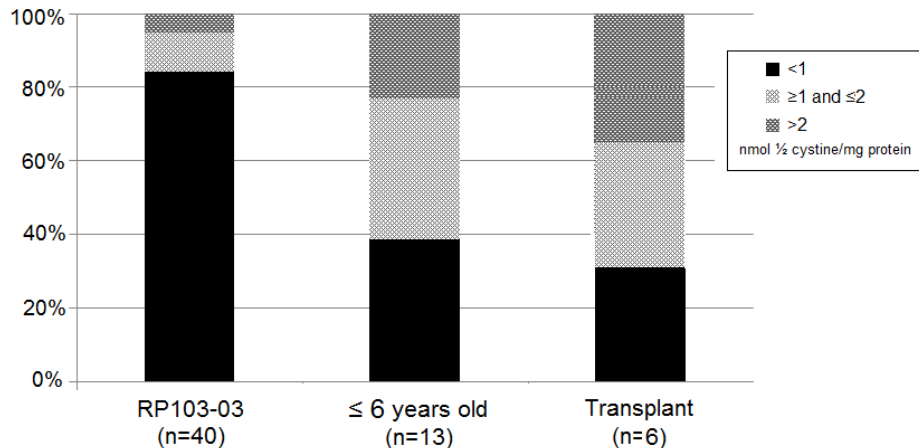
**Figure 10: Comparison of Baseline WBC Cystine Levels Between RP103-03 Patients and Patients ≤6 Years Old**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)  
 \* Mean ± Standard Deviation

The outlying value indicated by the red box is the baseline value of 10.60 for Subject 03009, which the Applicant reports was obtained in the context of treatment noncompliance with Cystagon prior to RP103-04 enrollment.

**Figure 11: Percentage of Patient Subgroups in Each Baseline WBC Cystine Group**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

Although mean WBC cystine levels for patients ≤6 years old were ≥1 nmol 1/2 cystine/mg protein for most analysis time points, a subset of these patients maintained WBC cystine levels <1 nmol 1/2 cystine/mg protein. As shown in Table 13 (summary table of WBC cystine data for patients ≤6 years old), the patients with the lowest baseline WBC cystine levels tended to maintain lower

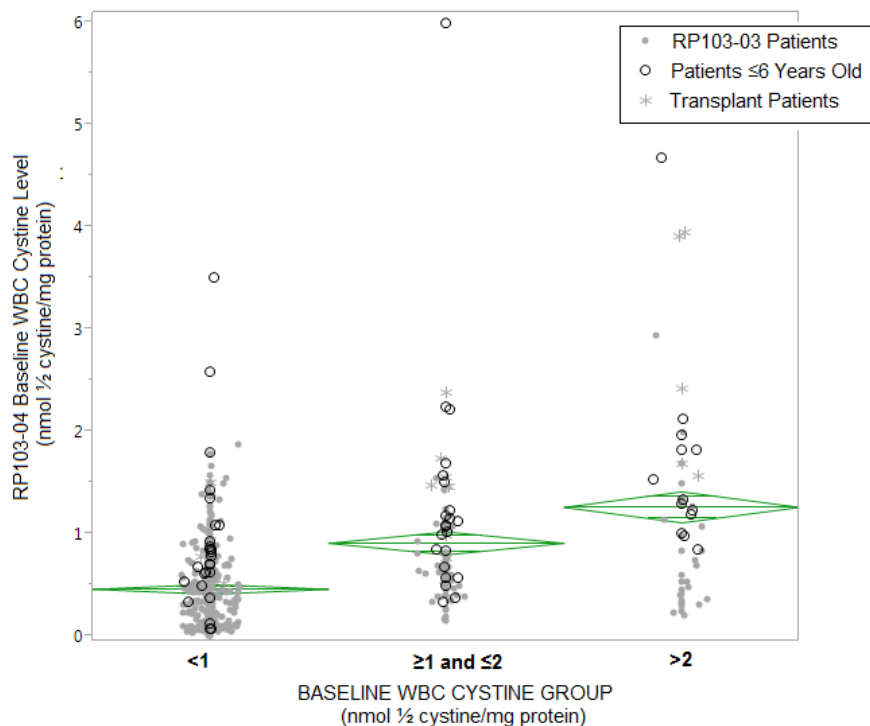
WBC cystine levels on subsequent assessment. In general, those patients  $\leq 6$  years old with lower baseline WBC cystine levels maintained lower levels on subsequent assessments. This pattern is also present in the RP103-03 patient subgroup. The relationship between baseline WBC cystine level and subsequent WBC cystine measurements for the entire RP103-04 clinical trial population is displayed graphically in Figure 12.

**Table 13: Patients  $\leq 6$  Years Old (n=13): WBC Cystine Levels (nmol  $\frac{1}{2}$  cystine/mg protein) for Adjusted Study Visits, Stratified by Baseline WBC Cystine Group**

Adjusted Study Visit (0.5 Hrs. Post Dose)	Baseline (nmol $\frac{1}{2}$ cystine/mg protein)			Overall
	<1	$\geq 1$ and $\leq 2$	>2	
<b>Baseline</b>				
N	5	5	3	13
Mean (SD)	0.47 (0.311)	1.41 (0.282)	2.96 (0.44)	1.41 (1.030)
Median	0.42	1.41	3.09	1.19
Min, Max	0.12, 0.96	1.11, 1.82	2.47, 3.33	0.12, 3.33
<b>Monthly 3</b>				
N	5	5	3	13
Mean (SD)	0.75 (0.380)	1.21 (0.669)	1.43 (0.487)	1.08 (0.565)
Median	0.63	1.17	1.34	1.09
Min, Max	0.33, 1.35	0.33, 2.21	1.00, 1.96	0.33, 2.21
<b>Monthly 6</b>				
N	5	5	3	13
Mean (SD)	1.32 (1.371)	2.35 (2.100)	2.57 (1.840)	2.00 (1.729)
Median	0.63	1.51	1.82	1.51
Min, Max	0.12, 3.50	0.85, 5.99	1.23, 4.67	0.12, 5.99
<b>Quarterly 1</b>				
N	5	5	3	13
Mean (SD)	0.73 (0.540)	1.02 (0.416)	1.47 (0.596)	1.01 (0.546)
Median	0.71	0.99	1.29	0.99
Min, Max	0.08, 1.43	0.57, 1.69	0.98, 2.13	0.08, 2.13
<b>Quarterly 2</b>				
N	5	4	3	12
Mean (SD)	1.19 (0.782)	0.92 (0.519)	1.19 (0.338)	1.10 (0.578)
Median	0.85	0.87	1.19	0.89
Min, Max	0.79, 2.59	0.37, 1.57	0.85, 1.53	0.37, 2.59
<b>Quarterly 3</b>				
N	5	2	1	8
Mean (SD)	0.68 (0.377)	0.84 (0.392)	1.82 (-)	0.86 (0.507)
Median	0.70	0.84	1.82	0.79
Min, Max	0.08, 1.09	0.57, 1.12	1.82, 1.82	0.08, 1.82
<b>Quarterly 4</b>				
N	1	1	0	2
Mean (SD)	0.49 (-)	0.50 (-)	0	0.49 (0.008)
Median	0.49	0.50		0.49
Min, Max	0.49, 0.49	0.50, 0.50		0.49, 0.50

(Source: Adapted from Applicant's Table 14, "Summary of WBC Cystine Concentrations Over Time (Subjects  $\leq 6$  Years of Age; PK/PD Population)", Interim Clinical Study Report page 78/201, NDA 203389, Module 5.3.5.2)  
 The last study visit (Adjusted Visit) completed by all 13 patients  $\leq 6$  years old was Quarterly 1, performed at Months 7 to 10, mean Month 9.

**Figure 12: Follow-up WBC Cystine Levels by Baseline WBC Cystine Group**

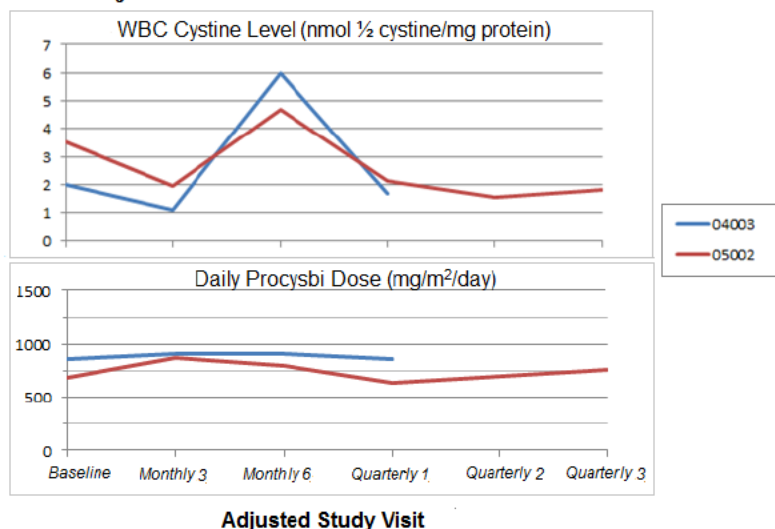


(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

For the 13 patients  $\leq 6$  years old enrolled in RP103-04, 12 had at least 1 assessment performed at  $\geq 12$  months of study participation. Mean ( $\pm$ SD) WBC cystine level for these patients at Month 12 (calculated using patients' first WBC cystine measurement at  $\geq$ Month 12, range Month 12 to Month 14) was 1.13 ( $\pm 0.56$ ) nmol  $\frac{1}{2}$  cystine/mg protein [baseline WBC cystine level 1.40 ( $\pm 1.08$ ) nmol  $\frac{1}{2}$  cystine/mg protein (n=12)], and at that study time point patients were receiving a mean ( $\pm$ SD) daily Procysbi dose of 912 ( $\pm 282$ ) mg/m<sup>2</sup>/day [initial Procysbi dose 814 ( $\pm 251$ ) mg/m<sup>2</sup>/day]. For the patients with WBC cystine level  $< 1$  nmol  $\frac{1}{2}$  cystine/mg protein, mean ( $\pm$ SD) daily Procysbi dose was 1062 ( $\pm 332$ ) mg/m<sup>2</sup>/day.

By the data cutoff date, 11 of the 13 patients (85%) had achieved WBC cystine levels  $< 1$  nmol  $\frac{1}{2}$  cystine/mg protein. Both patients who did not achieve WBC cystine level  $< 1$  nmol  $\frac{1}{2}$  cystine/mg protein (Subjects 04003 and 05002) experienced recurrent Procysbi-related gastrointestinal adverse reactions, which may have led to suboptimal dosage adjustments; however, no information is provided in RP103-04 Interim CSR to confirm this assumption. Serial WBC cystine measurements for these 2 patients are shown graphically in Figure 13. Prior to data cutoff, Subject 04003 had completed 3 follow-up study visits and Subject 05003 had completed 5 follow-up study visits. This is representative of the subgroup of patients  $\leq 6$  years old who completed an average (mean) 4.7 follow-up study visits per patient prior to data cutoff, as compared to an average (mean) of 12.6 follow-up study visits among RP103-04 patients. As a result, patients  $\leq 6$  years old had fewer opportunities for dosage adjustment to achieve optimal WBC cystine levels.

**Figure 13: WBC Cystine Levels and Daily Procysbi Doses Over Time for Subjects 04003 and 05002**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

This reviewer concludes that WBC cystine data in patients  $\leq 6$  years old are sufficiently similar to RP103-03 data to support the extrapolation of efficacy. The higher WBC cystine levels among patients  $\leq 6$  years old appears to be the effect of suboptimal Procysbi doses and fewer opportunities for dose adjustments in these patients, rather than differences in underlying disease characteristics. Additional data to support this conclusion is presented in Section 6.1.8.

### 6.1.5 Analysis of Secondary Endpoints(s)

This review includes a discussion of the two secondary endpoints—

- The evolution of Procysbi dose
- Cysteamine plasma concentration

The Applicant included the analyses for these endpoints in the efficacy section of the RP103-04 Interim CSR.

#### Evolution of Dose

The RP103-04 clinical trial protocol permitted Investigators to adjust Procysbi doses at each Study Visit following a review of available safety and PK/PD data, specifically if a patient does not achieve an appropriate WBC cystine reduction or does not tolerate their current Procysbi dose. As of the data cutoff date, 115 Procysbi dose adjustments were performed during RP103-04. All dose increases were performed in response to WBC cystine levels  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein; however, the reason for most dose reductions was not provided, and the Applicant indicates that most dose reductions were not triggered by Procysbi intolerance.

The evolution of Procysbi dose was evaluated in terms of (1) total daily dose corrected for body



surface area and (2) percentage of previous total daily Cystagon dose. It is important to note that international consensus treatment guidelines recommended a minimum cysteamine bitartrate dose of 1.3 grams/m<sup>2</sup>/day, and do not recommend reducing doses below this level unless patients experience medication intolerance, even in well-controlled patients.[12] In addition, a consensus statement from the NIH/Office of Rare Diseases conference on cystinosis in 2004 states that consideration should be given to targeting WBC cystine levels closer to normal levels (<0.2 nmol ½ cystine/mg protein) [52], since the levels necessary to prevent the progression of renal disease and the occurrence of extra-renal complications have not been established.[11] Thus, no comparable studies have been conducted with Cystagon to determine patients' minimum doses which maintain WBC cystine levels <1 nmol ½ cystine/mg protein.

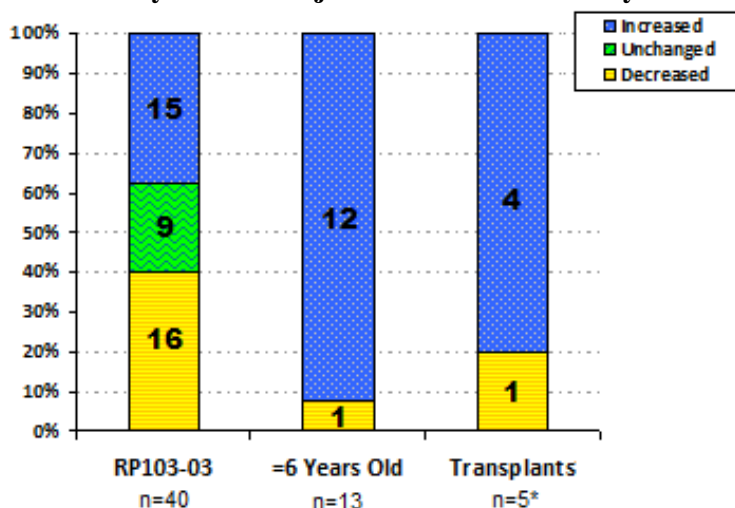
Analyses in this section of the review were used (b) (4)

- To inform dosing of Procysbi in patients 2 to 6 years of age for Supplement 10



At the time of data cutoff, 30/59 patients (51%) were receiving Procysbi doses higher than their initial dose at the start of RP103-04, while 19/59 (32%) were receiving lower doses, and doses remained unchanged for 10/59 patients (17%). The direction of Procysbi dose changes (i.e., most recent Procysbi dose prior to data cut-off vs. initial RP103-04 dose) are shown for each of the patient subgroups in Figure 14.

**Figure 14: Procysbi Dose Adjustments in RP103-04 by Patient Subgroup (Initial vs. Last<sup>†</sup> Dose)**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

<sup>†</sup> Procysbi dose at patient's last available assessment prior to data cutoff

\* One transplant patient was excluded from this analysis because the patient was found to be non-compliant and was withdrawn from RP103-04 prior to re-evaluation of initial Procysbi dosage, which did not yield any WBC cystine levels  $<1 \text{ nmol } \frac{1}{2} \text{ cystine/mg protein}$

Patients whose doses were unchanged or decreased were more likely to have previous daily Cystagon doses above the minimum recommended dose. In addition, these patients were generally older and, not surprisingly, had lower baseline WBC cystine levels. These are subjective observations. No statistical analyses could be performed to demonstrate statistical significance of these observations

**Table 14: Differences Between Patients for whom Procysbi Doses were Increased, Decreased, or Remained Unchanged During RP103-04 (N=58\*)**

		Increased Dose (n=31)	Unchanged Dose (n=9)	Decreased Dose (n=18)
<b>Baseline Cystagon Dose</b> (mg/m <sup>2</sup> /day)	mean (±SD)	1379 ± 466	1437 ± 241	1473 ± 332
	median	1286	1467	1463
	range	(741 – 2174)	(1136 – 1887)	(629 – 1947)
<b>Patient Age</b> (years)	mean (±SD)	9.1 (±5.9)	11.3 (±4.7)	13.2 (±6.0)
	median	7	9	12
	range	(2 – 28)	(6.5 – 20)	(5 – 32)
<b>Baseline cysteamine level</b> (mg/L)	mean (±SD)	0.52 (±1.12)	1.75 (±1.49)	0.53 (±0.66)
	median	0.20	1.5	0.27
	range	0.08 – 5.64	(0.34 – 4.00)	(0.08 – 2.46)
<b>Baseline WBC cystine level</b> (nmol $\frac{1}{2}$ cystine/mg protein)	mean (±SD)	1.21 (±1.05)	0.34 (±0.29)	0.96 (±2.4)
	median	0.87	0.27	0.33
	range	(0.06 – 4.34)	(0.03 – 0.96)	(0.05 – 10.6*)
<b>Change in Procysbi Dose</b> (%)	mean (±SD)	26.9 (±20.4)%	N/A	-16.6 (±13.1)%
	median	22.2%		-13.1%
	range	(+4/3 to +85.7%)		(-3.2 to -44.7%)

(Source: Reviewer's table using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

\* One transplant patient was excluded from this analysis because the patient was found to be non-compliant and was withdrawn from RP103-04 prior to re-evaluation of initial Procysbi dosage, which did not yield any WBC cystine levels  $<1 \text{ nmol } \frac{1}{2} \text{ cystine/mg protein}$

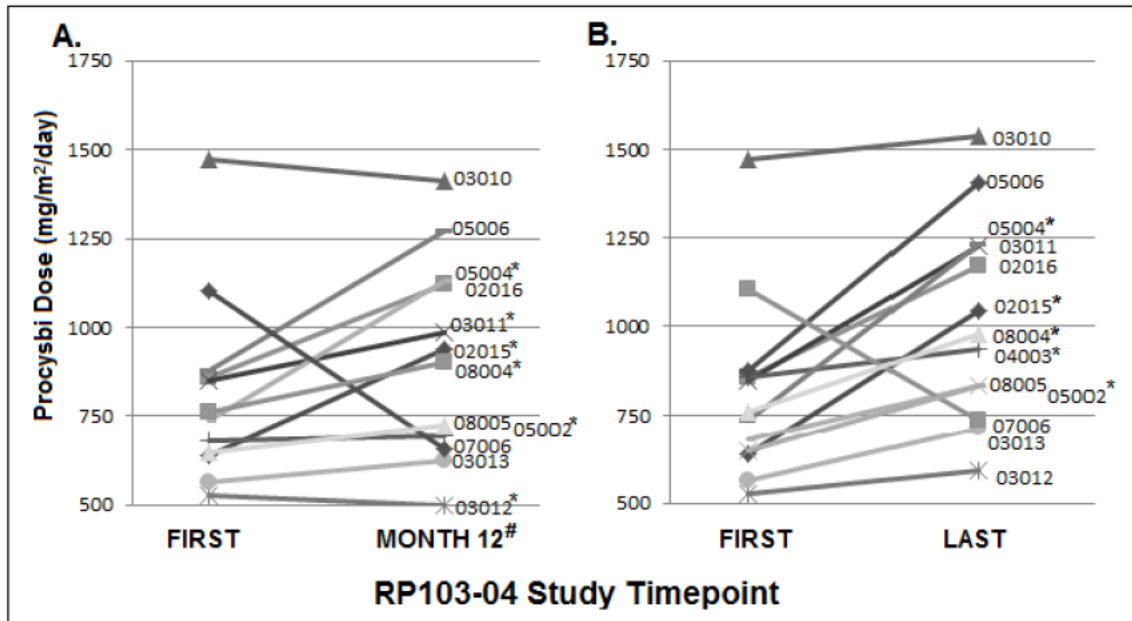
For the patients  $\leq 6$  years old, individual patient's Procysbi dose changes are shown in Figure 15. For 12/13 patients, Procysbi doses at data cutoff were higher than initial RP1-03-04 Procysbi doses. At "Month 12" (i.e., Month 12 (75%) of patients were receiving doses higher than their starting RP103-03 dose, and 6 of the 12 or the first assessment thereafter), data were available for 12/13 patients, and 6/12 patients had WBC cystine level  $\geq 1 \text{ nmol } \frac{1}{2} \text{ cystine/mg protein}$ . At patients' last assessment prior to data cutoff (range Month 10 to Month 17), 12 of the 13 patients (92%) were receiving a Procysbi daily dose higher than his/her starting Procysbi dose, and 5 of the 13 patients had WBC cystine level  $\geq 1 \text{ nmol } \frac{1}{2} \text{ cystine/mg protein}$ . For these 12 patients whose Procysbi doses at last assessment were higher than at the start of RP103-04, mean (±SD) dose increase was 33.6%.

In one patient, Subject 07006 (the only patient with decreased dose at last assessment), the

patient's dose was markedly decreased during study participation, affecting mean calculations for this subgroup. Several gastrointestinal adverse reactions were reported for this patient and may have led to this marked dose reduction; however, no reason is provided in the RP103-04 datasets or Interim Clinical Study Report.

Overall, these data support the conclusion that treatment response is similar between patients  $\leq 6$  years old and older patients, and differences in WBC cystine level between the groups are due to suboptimal doses. In other words, these data provide supportive evidence that patients  $\leq 6$  years old can achieve desirable WBC cystine levels when treated with adequate doses of Procybsi.

**Figure 15: Procybsi Dose Adjustments in Patients  $\leq 6$  Years Old During RP103-04 (Procybsi Daily Dose Corrected for Body Surface Area)**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)  
 \*Patient with WBC cystine level  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein at follow-up time point (i.e., "Month 12" or "Last")  
 # "Month 12" is defined as time point of Study Visit performed at Month 12 or the first visit thereafter (range study Month 12 to Month 14); 1 patient (Subject 04003) did not have a Study Visit at  $\geq$  Month 12.  
 "Last" is defined as the patient's last available assessment prior to data cutoff (range study Month 12 to Month 17).

(b) (4)

Summary statistics for Procybsi dose expressed as daily dose corrected for BSA and percentage of previous daily Cystagon dose are shown in Table 15.

**Table 15: First and Last Procysbi Doses (Dose Corrected for Body Surface Area and Ratio to Previous Cystagon Daily Dose) for RP103-04 Patient Subgroups**

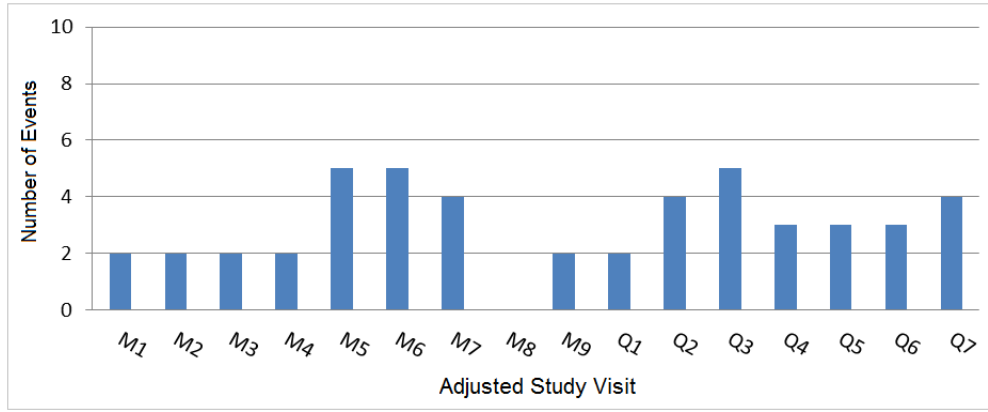
Procysbi Dose		PATIENT GROUP			
		All	RP103-03*	≤6 Years Old	Transplant
Ratio to Previous Cystagon dose	<b>First</b>				
	Mean (±SD)	0.82 (±0.16)	0.84 (±0.08)	0.75 (±0.02)	0.89 (±0.46)
	Median	0.86	0.87	0.74	0.80
	Range	0.66 – 1.83	0.69 – 1.05	0.67 – 0.88	0.66 – 1.83
	<b>Last</b>				
	Mean (±SD)	0.88 (±0.20)	0.85 (±0.21)	0.95 (±0.21)	0.88 (±0.16)
Median	0.87	0.85	0.94	0.90	
Range	0.39 – 1.63	0.39 – 1.63	0.56 – 1.25	0.66 – 1.08	
Total Daily Procysbi Dose (mg/m <sup>2</sup> /day)	<b>First</b>				
	Mean (±SD)	1133 (±322)	1277 (±246)	814 (±251)	863 (±245)
	Median	1169	1256	761	899
	Range	526 – 1923	695 – 1923	526 – 1474	545 – 1154
	<b>Last</b>				
	Mean (±SD)	1213 (±381)	1319 (±374)	1019 (±283)	923 (±329)
Median	1193	1275	978	853	
Range	549 – 2283	549 – 2283	592 – 1538	594 – 1393	

(Source: Reviewer's table using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

At baseline, 6 (15%) of the RP103-03 patients had WBC cystine level  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein. During participation in RP103-04, 20 of the 40 patients—5 of the 6 patients with elevated baseline WBC cystine and 15 patients with baseline WBC cystine  $< 1$  nmol  $\frac{1}{2}$  cystine/mg protein—had at least one WBC cystine follow-up assessment with a level  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein (mean 2.4 events per patient, range 1 to 9 events). For these RP103-03, WBC cystine levels  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein were evenly distributed across study visits (Figure 17), and 28/48 (42%) events occurred the patients with desirable baseline level.

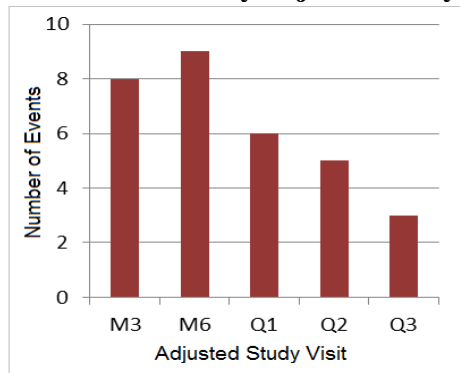
Similarly, 3 of the 5 patients  $\leq 6$  years old with baseline WBC cystine  $< 1$  nmol  $\frac{1}{2}$  cystine/mg protein had at least 2 follow-up WBC cystine levels  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein. This indicates that maintenance of WBC cystine levels in the target range requires maintenance of adequate Procysbi doses. However, unlike the RP103-03 patients whose doses were more likely to be reduced and WBC cystine levels  $\geq 1$  occurred in patients with previously well-controlled levels, the patients  $\leq 6$  years old overall showed gradual improvement in WBC cystine levels as doses were incrementally increased. (Figure 18)

**Figure 17: Number of WBC Cystine Levels  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein in RP103-03 Patients by Adjusted Study Visit**



(Source: Reviewer’s figure using Applicant’s Analysis Datasets, NDA 203389, Module 5.3.5.2)

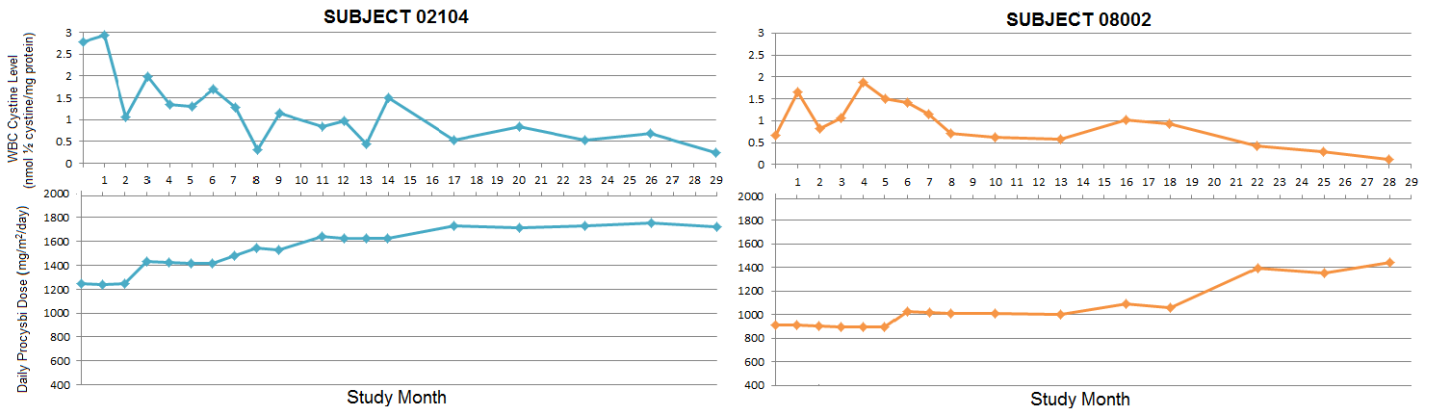
**Figure 18: Number of WBC Cystine Levels  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein in Patients  $\leq 6$  Years Old by Adjusted Study Visit**



(Source: Reviewer’s figure using Applicant’s Analysis Datasets, NDA 203389, Module 5.3.5.2)

In RP103-03, 2 patients (Subject 02104 and Subject 08002) had baseline WBC cystine levels  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein—1.22 and 1.01 nmol  $\frac{1}{2}$  cystine/mg protein, respectively. These levels represent the last levels obtained on Cystagon treatment prior to initiation of Procysbi treatment at a daily dose equal to ~70% of their previous Cystagon daily dose. Both Subject 02104 and 08002 had a disproportionate number of WBC cystine assessments  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein (9 and 7 assessments, respectively) during RP103-04 (Figure 19), despite the mild degree of WBC cystine elevation above the maximum target level, providing additional evidence, though anecdotal, of the fragile nature of disease control in nephropathic cystinosis.

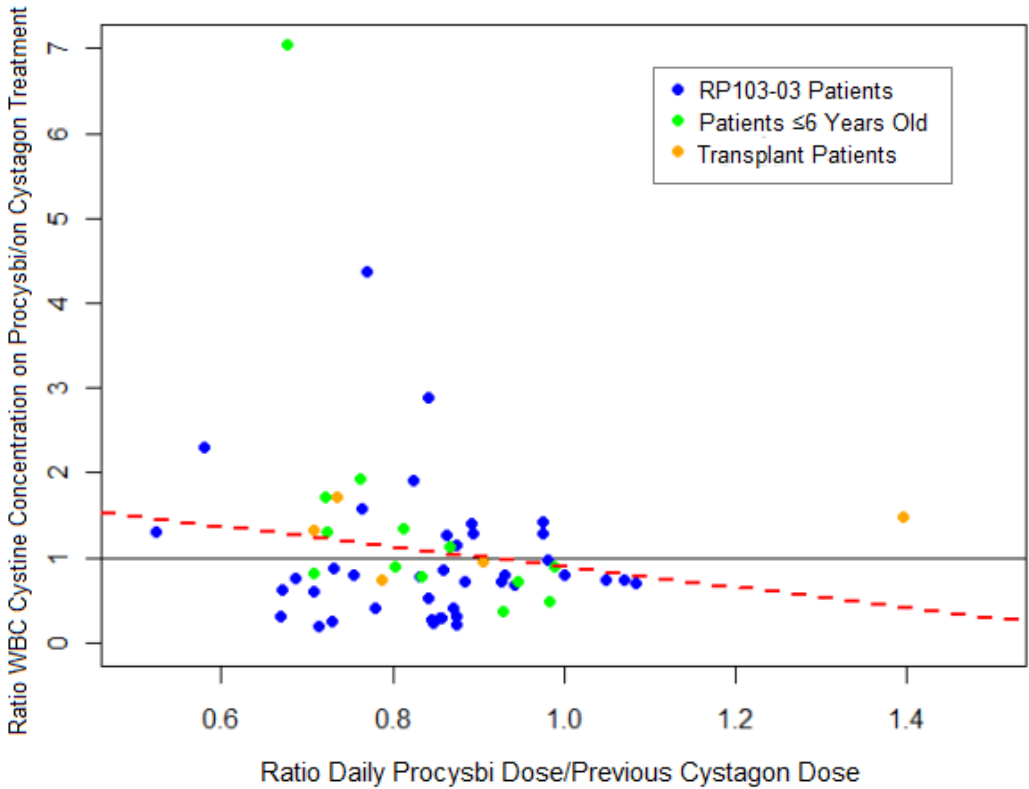
**Figure 19: WBC Cystine Level and Procysbi Dose for Subjects 02104 and 08002**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

According to analyses by the Pharmacometrics Reviewer, the average Procysbi doses required to achieve WBC cystine level similar to levels achieved with Cystagon (horizontal line with y-value 1) are >91% of previous daily Cystagon doses (Figure 20).

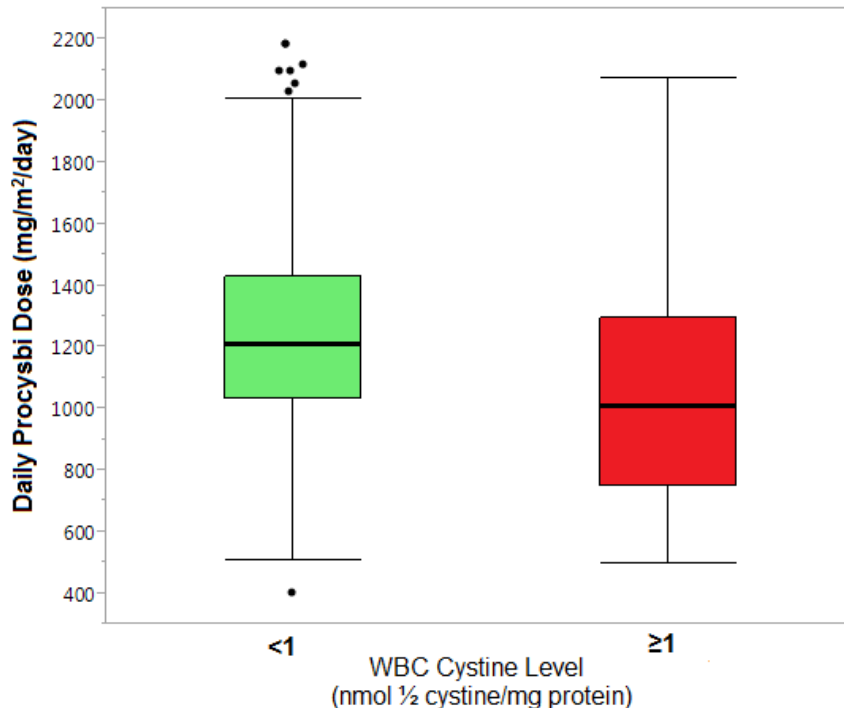
**Figure 20: Procysbi Doses Relative to Cystagon Doses Needed to Achieve the Same WBC cystine Concentration Achieved on Cystagon**



(Source: Pharmacometrics reviewer's Figure 4, Clinical Pharmacology Review dated June 29, 2015)

In addition, the mean Procysbi daily dose (corrected for BSA) that achieved WBC cystine levels  $<1$  nmol  $\frac{1}{2}$  cystine/mg protein (i.e., the mean of all Procysbi doses corresponding to WBC cystine levels) for the entire RP103-04 population is 1234 ( $\pm 326$ ) mg/m<sup>2</sup>/day vs. 1046 ( $\pm 354$ ) mg/m<sup>2</sup>/day (Figure 21), corresponding to the recommended starting maintenance dose in the prescribing information. Because poor disease control in patients with nephropathic cystinosis, even for brief periods, can lead to irreversible tissue damage [33], selection of adequate doses which maintain sustained intracellular cystine depletion is critical. Thus, in the absence of safety concerns, recommended doses should be selected based on the doses demonstrated to achieve desirable WBC cystine levels in most patients.

**Figure 21: Comparison of Patients' Procysbi Daily Doses (Corrected for Body Surface Area) Administered at the time of WBC Cystine Levels  $<1$  vs.  $\geq 1$  nmol  $\frac{1}{2}$  cystine/mg protein**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

(b) (4)

### 6.1.6 Other Endpoints

The following exploratory endpoints were included in the interim efficacy analyses for RP103-04:

- Growth (height and weight, with age- and sex-based Z-scores)
- Estimated glomerular filtration rate (eGFR)\*
- Quality of life (tools: PedsQL Version 4.0 Generic core score\*)
- Swallowing difficulty by Visual analog scale (VAS)\*

#### **Linear Growth**

Although not pre-specified as a clinical trial endpoint, the Applicant included analyses of height Z-scores among the efficacy data for RP103-04. Based on these data, growth velocity was generally maintained in all patient subgroups during RP103-04, suggesting that linear growth is not adversely affected by Procysbi treatment. No additional conclusions can be drawn from these data. Because the evaluation of linear growth was not pre-specified as a clinical trial efficacy endpoint and assessment procedures were not included in the RP103-04 protocol, these analyses would be considered exploratory, at most. However, the use of growth hormone among clinical trial patients (n=20, including 3 patients  $\leq 6$  years old) confounds interpretation of these data.

#### **Quality of Life**

Quality of life was a pre-specified exploratory endpoint for RP103-04. In pediatric patients (n=52), serial assessments were performed using the PedsQL 4.0 Generic Core Scale. The PedsQL 4.0 includes 5-point likert scales for 4 functional areas (physical, emotional, social, and school functioning), which can be used to calculate a total score or can be translated into 2 summary scores—psychosocial health and physical health. All item scores and summary scores are calculated based on a maximum score of 100.

In the Interim Study Report, the Applicant reported mean total scores and scores for the four functional areas. For the RP103-03 patients, change in total score from baseline ranged from 2.1 to 4.4 points out of 100, with statistical significance reported for 2 of the 5 time points. For the patients  $\leq 6$  years old, change in total score from baseline was not statistically significant at any time point (range 0 to 7.8 points out of 100). Overall, results were inconsistent and poorly sustained over time.

This instrument not been validated for use as a clinical trial endpoint in this patient population,



and the meaningfulness of subjective data cannot be determined in the absence of a control group. Therefore, these data were reviewed to ensure consistency with efficacy data, but did not contribute to overall efficacy determinations.

**Table 16: Change in PedsQL 4.0 Generic Core Scales from Baseline  
 (Maximum Score 100 for Total Score and for All Individual Item Scores)**

	Physical	Emotional	Social	School	Total
RP103-04 PATIENTS					
Monthly 1	0.9	5.2*	4.6	5.1*	3.5*
Monthly 6	0.2	1.1	2.7	5.6*	2.1
Quarterly 2	2.7	3.9*	3.6	8.7*	4.4
Quarterly 4	4.3	1.7	3.9	6.3*	3.8*
Quarterly 6	2.0	0.1	2.4	4.8*	2.4
PATIENTS ≤6 YEARS OLD					
Monthly 3	8.4	0.6	-0.4	1.2	3
Monthly 6	7.7	14.2	-0.4	1.0	5.7
Quarterly 2	2.7	5.8	-7.4	4.1	0
Quarterly 4 <sup>†</sup>	10.5	8.8	1.3	12.5	7.8

(Source: Reviewer's table using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

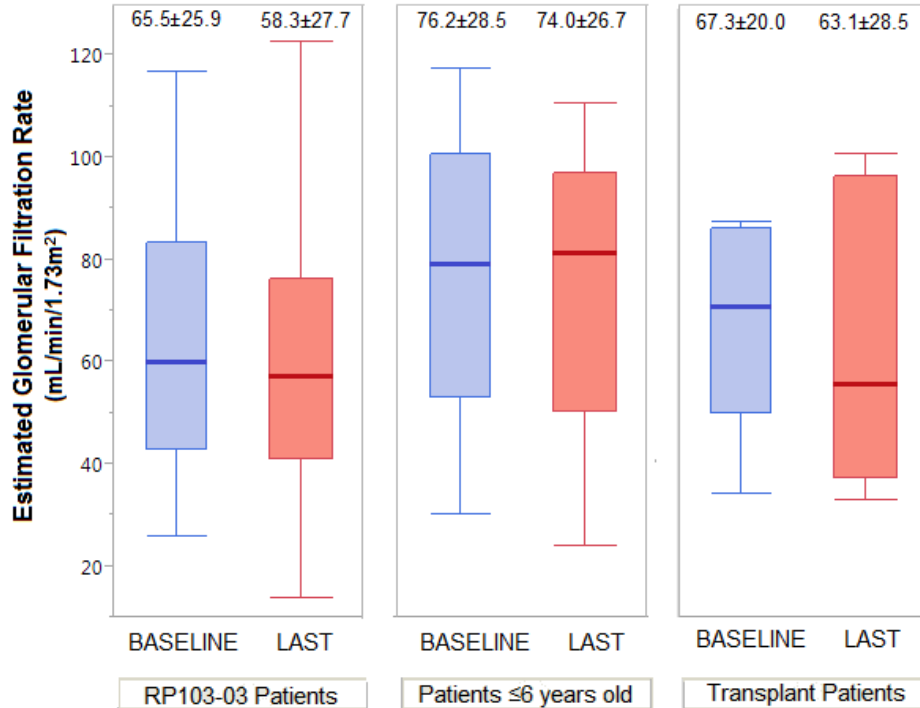
\*p-value <0.5

<sup>†</sup> Only 8/12 patients completed this assessment

### **Estimated Glomerular Filtration Rate (eGFR)**

Overall, mean estimated glomerular filtration rate (eGFR) for RP103-03 patients and patients ≤6 years old remained unchanged during RP103-04. For the 5 transplant patients with available data, mean eGFR decreased but interpatient results were highly variable, likely due to episodes of acute rejection unlikely related to Procysbi treatment (Figure 23).

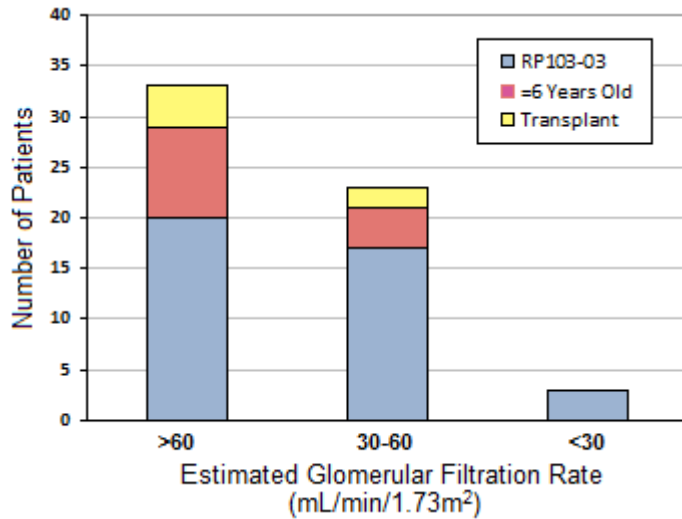
**Figure 23: Change in Estimated Glomerular Filtration Rate (eGFR) for RP103-04 Patient Subgroups**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

Baseline eGFR was more variable in the RP103-03 group, which included 3 patients with eGFR <30 mL/min/1.73m<sup>2</sup> (Subjects 03004, 07004, 02010). Due to the advanced degree of renal damage, declining renal function would be expected in patients with low baseline eGFR, regardless of WBC cystine level. The RP103-03 patient group included a greater percentage of patients with baseline eGFR near 30 mL/min/1.73m<sup>2</sup>.

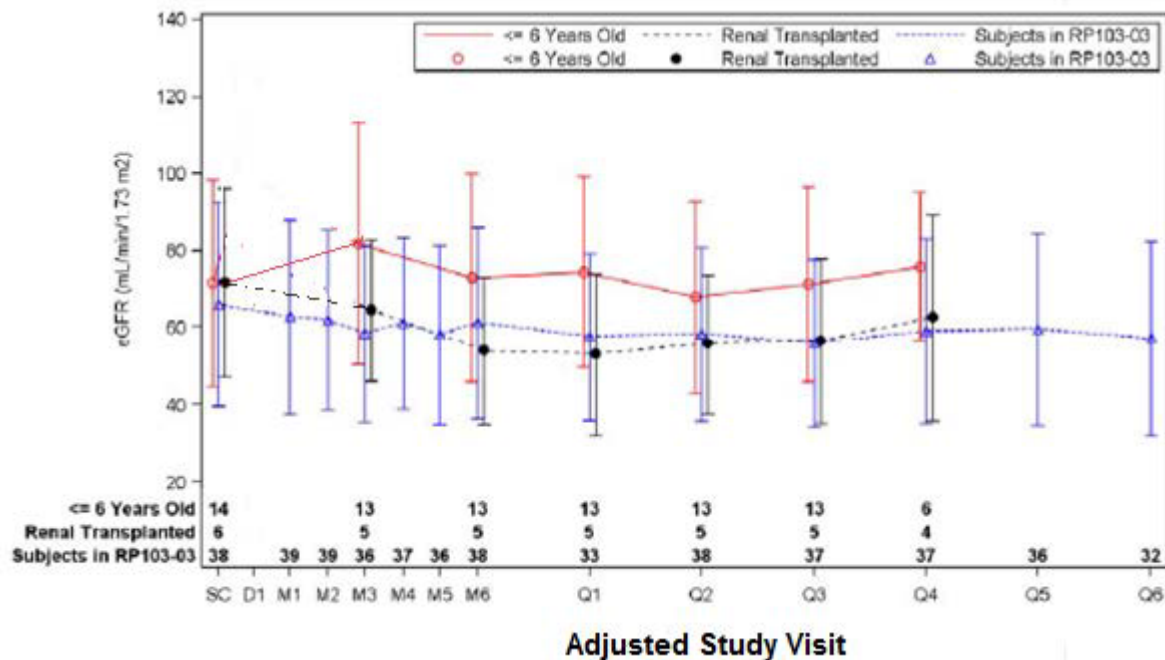
**Figure 24: Baseline Estimated Glomerular Filtration Rate**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

Several episodes of transient creatinine elevations occurred during RP103-04, typically associated with dehydration. This would be expected in a patient population with uncontrolled renal fluid and electrolyte losses and variable degree of underlying renal insufficiency.

**Figure 25: Evolution of eGFR (mL/min/1.73 m<sup>2</sup>) for RP103-04 Patient Subgroups**

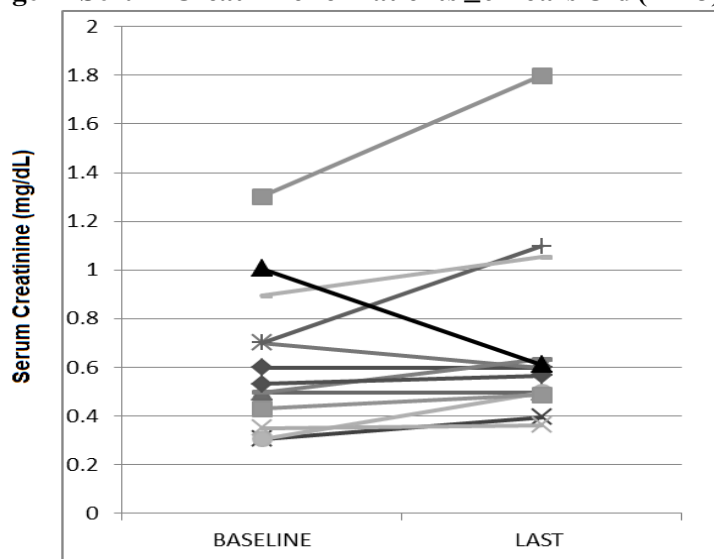


(Source: Applicant's Figure 7, "Evolution of eGFR (mL/min/1.73 m<sup>2</sup>) over Time (Collected Visits)", RP103-04 Interim Clinical Study Report page 94/201, NDA 203389, Module 5.3.5.2)

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For the patients  $\leq 6$  years old, most patients demonstrated relatively preserved renal function over time (Figure 26). For Subject 02016, who was 6 years of age at enrollment with a baseline eGFR 30.2 mL/min/1.73m<sup>2</sup>, the increase in serum creatinine from 1.30 to 1.80, equivalent to a 38% in renal function, would not be an unexpected decline in this patient.

**Figure 26: Change in Serum Creatinine for Patients  $\leq 6$  Years Old (n=13)**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

For the RP103-03 patients, 6 patients were identified whose decline in renal function appeared greater than expected based on their baseline eGFR.

**Table 17: Patients with  $>50\%$  Decline in Renal Function between Baseline and Last Available Serum Creatinine Measurements (n=6)**

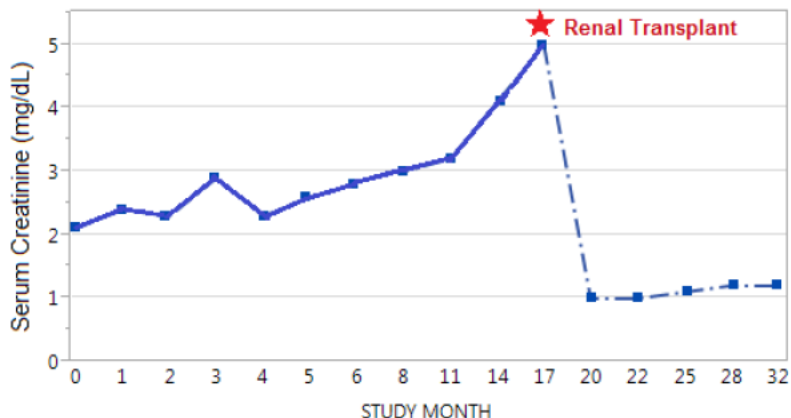
Patient	Age (yrs)	Serum Creatinine (mg/dL)		Fold change	Interval (months)
		Baseline	Last available		
03002	15.3	1.60	3.40	2.13	31.6
03101	9.4	0.40	1.10	2.77	26.8
06003	11.5	1.41	3.65	2.58	26.9
07002	19.0	1.64	4.07	2.48	27.0
08002	14.1	0.74	1.87	2.54	30.8
09001*	15.5	1.07	5.14	4.78	20.2

(Source: Reviewer's table using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

\*Patient withdrawn from the clinical trial due to the decline in renal function

In addition to the patients listed in Table 17, one of the RP103-03 patients with baseline eGFR  $<30$  mL/min/1.73m<sup>2</sup> (Subject 03004) progressed to end stage renal disease during RP103-04 and underwent renal transplantation during study participation. Of note, this patient subsequently developed acute renal allograft rejection. This patient's serum creatinine levels during RP103-04 are displayed in Figure 27.

**Figure 27: Serum Creatinine Values for Subject 03004**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

### **Swallowing Difficulty**

Pain-associated swallowing difficulty was assessed using a 10-point Visual Analog Scale (VAS), with a score of 0 representing "no pain with swallowing" and a score of 10 representing the "highest pain with swallowing." On initial assessment, the score for 36 (62.1%) of the 58 completed assessments was zero and only 10/58 (13.7%) had a score greater than 2. In a population of previously-treated patients without notable baseline abnormalities and without a concurrent control group, any changes in these data are not interpretable.

### **6.1.7 Subpopulations**

Due to the small patient population, no additional subpopulation analyses (i.e., sex, race) were performed.

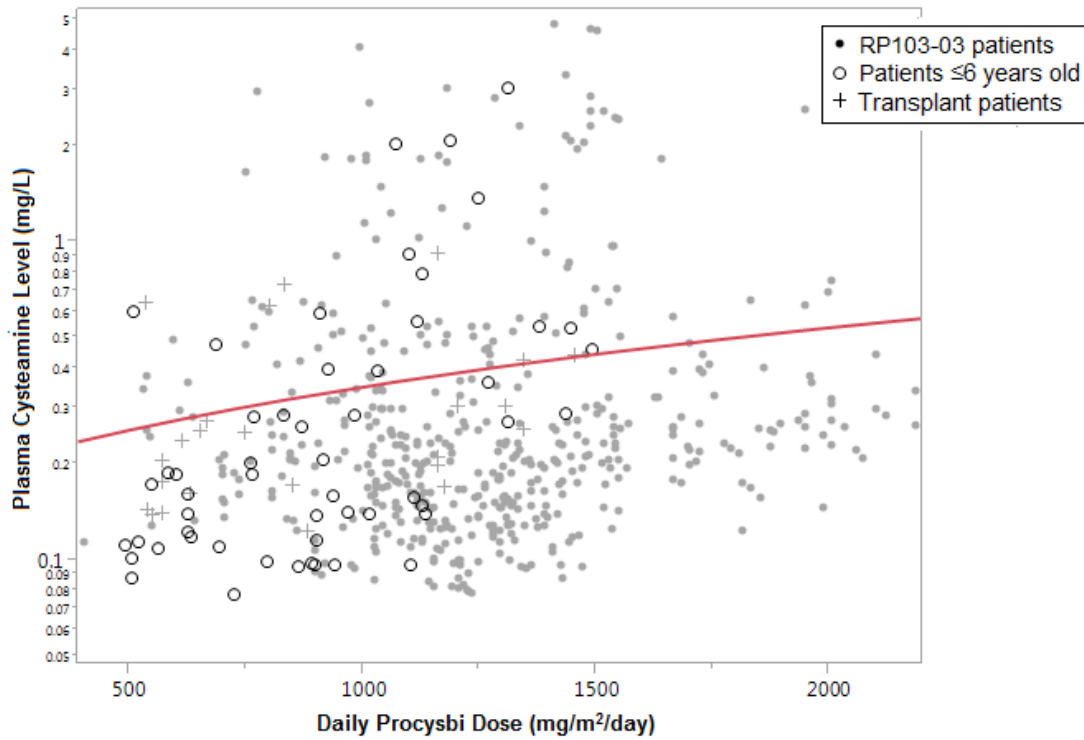
### **6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

Exposure-response, dose-exposure, and dose-response analyses were performed to support the extrapolation of Procysbi efficacy from data in older patients and inform the dosing of Procysbi in these patients. Exposure-response analyses are discussed in Section 4.4.3.

The scatterplots in Figure 28 and Figure 29 show the dose-exposure relationship using all available C<sub>30</sub> plasma cysteamine levels and the corresponding Procysbi doses (corrected for patient BSA). In Figure 30, the overlap between data for patients ≤6 years old and the rest of the clinical trial population is highlighted, demonstrating similar dose-exposure relationships across patient subgroups. Figure 14 dose-exposure data based on the WBC cystine level obtained concurrently with plasma cysteamine levels. The pattern of exposure-response data patients ≤6 years old is similar to the pattern for WBC cystine levels ≥1 nmol ½ cystine/mg protein, supports the conclusion that patients ≤6 years old have similar responses to treatment as older patients,

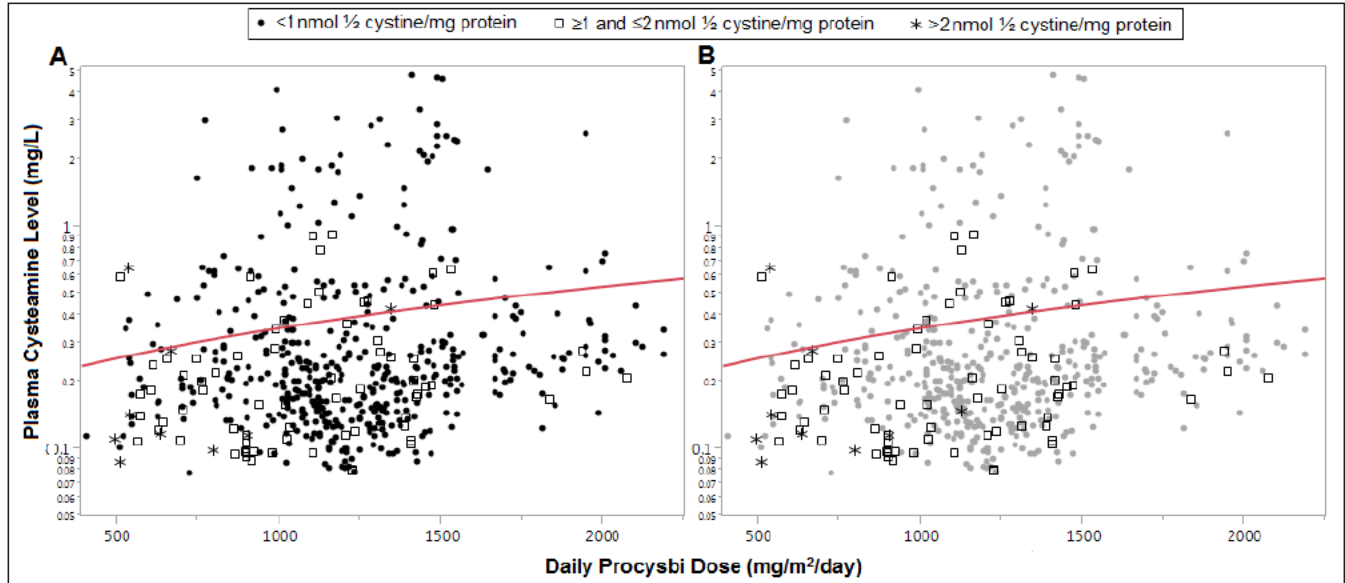
and differences in response in the younger patient subgroup are due to suboptimal dosing rather than differences in baseline disease characteristics.

**Figure 28: Procysbi Dose (Corrected for Body Surface Area) vs. Exposure (Plasma Cysteamine Level): Comparison of Patient Subgroups**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

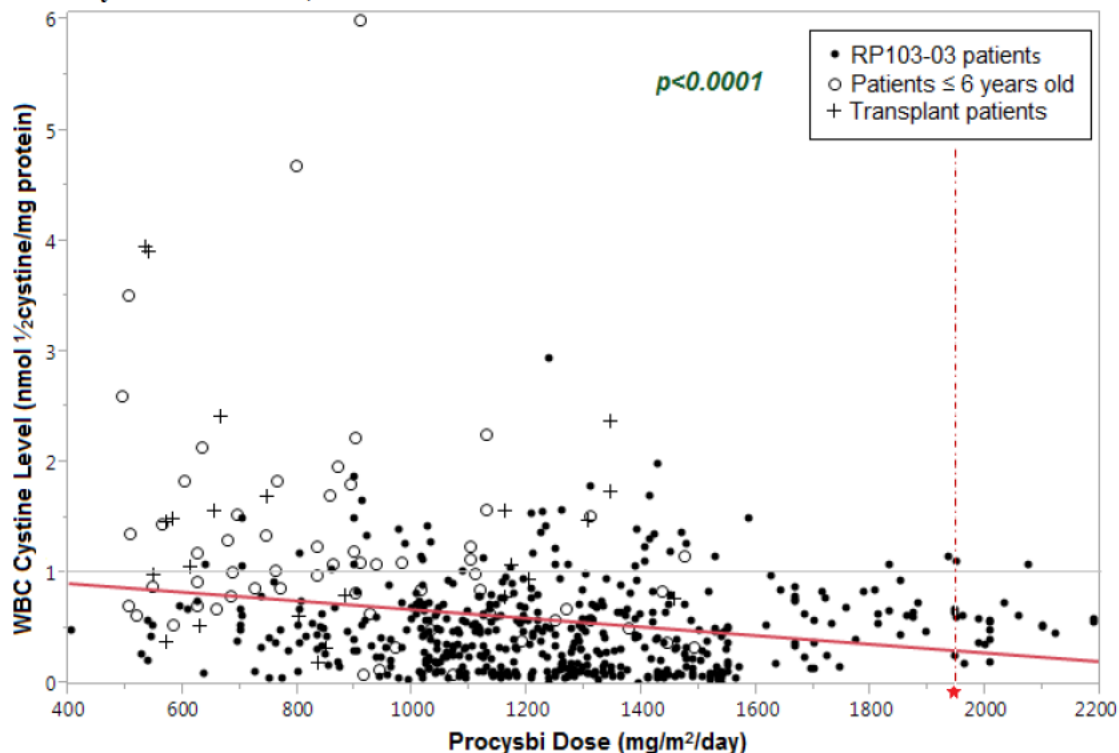
**Figure 29: Procysbi Dose (Corrected for Body Surface Area) vs. Exposure (Plasma Cysteamine Level): Comparison of WBC Cystine Levels**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

In clinical practice, WBC cystine levels are used to individualized patients' cysteamine bitartrate doses for optimal disease control. Therefore, this PD data may be more informative than PK data to inform dosing for labeling. Figure 30 is a scatterplot of dose-response data using all available follow-up WBC cystine levels and the corresponding Procysbi doses (corrected for patient BSA). Based on these data, the dose-response relationship is similar between patients ages 2 to 6 years old and the RP103-03 patients. Therefore, this reviewer recommends the same Procysbi dosing for patients ages 2 to 6 years old as the older population for whom Procysbi had already been approved. For patients without prior treatment of cysteamine bitartrate, the recommended starting maintenance daily dose of Procysbi is 1300 mg/m<sup>2</sup>/day. For patients switching from immediate-release cysteamine bitartrate, the Applicant proposes (b) (4)

**Figure 30: Procysbi Dose (Corrected for Body Surface Area) vs. Exposure (Plasma Cystine Level)**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

In concurrence with recommendations from the Clinical Pharmacology review team, this reviewer concludes that the starting Procysbi daily dose in patients age  $\geq 2$  years old switching from immediate-release cysteamine bitartrate should equal to 100% of the patient's previous Cystagon daily dose.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Patients treated with adequate doses of Procysbi appeared to achieve and maintain WBC cystine levels within therapeutic target of  $< 1$  nmol  $\frac{1}{2}$  cystine/mg protein. There did not appear to be an evidence of patients developing tolerance to Procysbi.

### 6.1.10 Additional Efficacy Issues/Analyses

None



## 7 Review of Safety

### Safety Summary

The overall safety profile of Procysbi in Study RP103-04 is comparable between patients ages 2 to 6 years old and patients greater than 6 years old previously treated with immediate-release cysteamine bitartrate. Previously, the safety data of Procysbi in patients  $\geq 6$  years old was obtained from Study RP103-03, in which patients only received 3 weeks of treatment with Procysbi. Therefore, under the 505(b)(2) regulatory pathway, the FDA relied upon the previous determination of safety for the listed drug, Cystagon (immediate-release cysteamine bitartrate) to characterize the safety profile of Procysbi and support its approval.

No serious or unexpected adverse reactions occurred in patients ages 2 to 6 years old during Study RP103-04. As with other cysteamine products, gastrointestinal symptoms represented the majority of adverse reactions in patients ages 2 to 6 years old, and no patients in this subgroup discontinued study participation due to adverse reactions.

For the RP103-03 patients, the safety of treatment with Procysbi during RP103-04 was evaluated for up to 34.2 months [mean ( $\pm$ SD) duration of 26.8 ( $\pm$ 6.5) months]. No new safety concerns were identified for these patients. One unexpected adverse reaction occurred in these patients—decline in renal function in one patient leading to study discontinuation; however, this event is considered sufficient to change the safety profile of Procysbi. The other adverse reactions experienced by these patients have previously been associated with cysteamine treatment and are included in the prescribing information. Based on RP103-04, the safety profile of Procysbi does not seem to differ from other cysteamine-containing medications.

### 7.1 Methods

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary source of safety data was Study RP103-04, the ongoing, open-label, single-arm clinical trial of Procysbi, with a cutoff date for interim analyses of July 10, 2013. The safety population includes all patients who received at least 1 dose of Procysbi in RP103-04. In this case, the safety dataset is identical to the PK/PD dataset used for efficacy analyses—59 patients from RP103-04, consisting of 40 RP103-03 patients, 13 patients  $\leq 6$  years old, and 6 renal transplant patients.

#### 7.1.2 Categorization of Adverse Events

An adverse event (AE) was defined as any disturbance of general health status, subjective and objective disease symptoms (including laboratory abnormalities), and accidents observed in the context of the clinical trial, irrespective of a possible causal relationship with the administration of the study drug. AEs could be volunteered, elicited, or noted on physical examination or safety

assessments. Verbatim terms of adverse events (AEs) were coded by the Applicant using MedDRA System/Organ/Class (SOC) and Preferred Term (PT) designations.

A treatment emergent adverse event (TEAE) was defined as an AE that is reported after a dose of study drug.

A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (life threatening refers to an event in which the subject is at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe);
- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect; or
- Is medically significant, and though not included in the above list, is an important medical event that may jeopardize the subject or require medical intervention to prevent one of the outcomes listed above.

Discontinuation of study drug or conducting additional diagnostic evaluations, does not, by themselves, satisfy the criterion for a medically significant event.

AEs were also categorized based on the following assessments by the Investigator:

- Severity- grading categorized according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 [Cancer Therapy Evaluation Program, 2003]
- Treatment-emergent (yes/no): AE that emerged during treatment in study RP103-04, having been absent pretreatment, or worsened relative to the pretreatment state
- Causality: based on associative connections (time\_or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and absence of alternative explanations, with the following classifications:
  - Not related: Time relationship with Study drug administration is nonexistent or other factors, certain or probable, to have been causative
  - Unlikely: Time relationship with Study drug administration is doubtful or other factors, certain or probable, to have been causative.
  - Possible: Time relationship with Study drug administration may exist. Other possible causative factors may exist (e.g., concurrent disease or concomitant medication). Improvements on rechallenge or dose reduction (if performed) may or may not have been seen.
  - Probable: Time relationship with Study drug administration likely exists. No other possible causative factors may exist (not reasonably explained by the subject's

known clinical state or concomitant medication). Improvements on rechallenge or dose reduction (if performed) have occurred. Recurrence of symptoms on rechallenge (if performed) has occurred. A specific laboratory investigation (if performed) has confirmed the relationship.

- Definite: Those events for which there is no shadow of doubt that they are a consequence of administration of the test product. It is likely that such events will be widely documented and generally accepted as having association with the test product or that they reoccurred after rechallenge (if performed).

### **Independent Clinical Reviewer Assessments**

In order to accurately assess the frequency of specific adverse reactions and the prevalence of organ system-wide toxicities, this clinical reviewer compared verbatim terms with the applicant's coded/preferred term and assigned SOC. Revisions were made to (1) combine terms with similar meaning (e.g., bromhidrosis and abnormal body odor, abdominal discomfort and abdominal pain) and (2) group related AEs under the same SOC.

In the absence of a comparator control group, identifying the adverse events which represent treatment-related adverse reactions relies on assessments of causality. Therefore, this clinical reviewer performed an independent assessment of causality taking into consideration the following factors:

- Known association between event and cysteamine
- Lack of alternate explanation for event
- Lack of resolution of event
- Recurrent episodes of event
- Prolonged duration of event
- Description of event as recurrent, chronic, etc.
- Temporal relationship between onset/worsening of event and initiation or increased dose of Procysbi
- Temporal relationship between improvement of event and Procysbi dose reduction/discontinuation
- Occurrence of other similar adverse events
- Investigator assessment of causality as possibly, probably, or definitely related to treatment

When necessary to perform these assessments, additional narratives for non-serious adverse events were requested and provided by the Applicant.

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

The Applicant provided an Integrated Summary of Safety, which included data from all clinical trial patients. For this review, analyses were primarily based on RP103-04 data. However, results were compared across clinical trials to evaluate for new or subgroup-specific safety signals.

## 7.2 Adequacy of Safety Assessments

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

Table 18 summarizes Procysbi exposure in RP103-04 for the 3 patient subgroups. As of the cutoff date of July 10, 2013, mean length of Procysbi treatment in Study RP103-04 was 26.8 months for RP103-03 patients (range 1.9 to 34.2 months) vs. 16.8 months for the 19 newly enrolled patients (range 1.1 to 19.6 months). RP103-03 patients received a mean ( $\pm$ SD) daily Procysbi dose of 1234 ( $\pm$ 300) mg/m<sup>2</sup>/day vs. 875 ( $\pm$ 269) mg/m<sup>2</sup>/day received by newly enrolled patients. The fact that mean doses received by newly enrolled patients were suboptimal was taken into consideration when performing safety analyses. However, based the totality of data and reliance on safety data from other cysteamine products under the 505(b)(2) pathway, this reviewer considered the available data and patient population sufficient for safety assessments.

**Table 18: Procysbi Exposure in RP103-04 (N=59 patients)**

		RP103-03 (n=40)	$\leq 6$ Years Old (n=13)	Transplant (N=6)
<b>Average* Daily Procysbi Dose</b> (mg/m <sup>2</sup> /day)	Mean ( $\pm$ SD)	1234 ( $\pm$ 300)	897 ( $\pm$ 260)	828 ( $\pm$ 290)
	Median	1195	860	708
	Range	630 — 2063	516 — 1444	596 — 1321
<b>Duration of exposure in RP103-04</b>				
<b>Days</b>	Mean ( $\pm$ SD)	814 ( $\pm$ 199)	524 ( $\pm$ 59)	431 ( $\pm$ 200)
	Median	874	539	520
	Range	57 — 1040	436 — 596	34 — 556
<b>Months</b>	Mean ( $\pm$ SD)	26.8 ( $\pm$ 6.5)	17.2 ( $\pm$ 1.9)	14.2 ( $\pm$ 6.6)
	Median	28.7	17.7	17.1
	Range	1.9 — 34.2	14.3 — 19.6	1.1 — 18.3

(Source: Reviewer's table using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

\* To determine Average Daily Procysbi dose, the mean total daily Procysbi dose (corrected for body surface area) was determined for each RP103-04 patient (i.e., sum of all daily Procysbi doses received by an individual patient  $\div$  number of days on Procysbi treatment); therefore, each patient was weighted equally when determining subgroup means, irrespective of the total number of Procysbi doses received by an individual patient.

## 7.2.2 Explorations for Dose Response

Because Procysbi dosing in RP103-04 lacked both fixed dosing and randomization of patients to dose groups, no formal assessments for dose-related safety were performed. The frequency of dose changes (total 115 dose changes for the 59 clinical trial patients) points and lack of standardized dosing periods precluded comparisons of safety data with both medication dose and exposure. Therefore, any relationships identified between medication doses (absolute dose and/or change in dose) and adverse reactions are anecdotal. In the case narratives throughout Section 7.3, dose changes with a temporal relationship to the onset/exacerbation/alleviation of adverse reactions are described, but conclusions based on these subjective data are limited.

## 7.2.3 Special Animal and/or In Vitro Testing

None

## 7.2.4 Routine Clinical Testing

RP103-04 safety assessments were performed at all Study Visits and consisted of the following:

- Adverse events
- Concomitant medications review
  - Separate analyses of the use of gastric acid reducing (GAR) medications
- Vital signs/physical examination
- Laboratory studies (hematology, chemistry, urinalysis)
- Electrocardiogram (ECG)

## 7.2.5 Metabolic, Clearance, and Interaction Workup

No new studies of Procysbi metabolism and clearance were conducted for this review.

During this review cycle, consideration was given to the effects of medications, foods, and beverages which alter gastric pH on the pharmacokinetics and effectiveness on Procysbi. Only 1 drug interaction study, RP103-HLTA 009, a bioequivalence study comparing Procysbi pharmacokinetics with and without concomitant proton pump inhibitor administration, was reviewed by the Dr. Insook Kim, Clinical Pharmacology reviewer (see review dated June 29, 2015)

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

The routine safety assessments in RP103-04 were adequate to evaluate for adverse events associated with cysteamine administration. Safety analyses for these adverse reactions are discussed in Section 7.3.5 (Submission-Specific Primary Safety Concerns)

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Procysbi (delayed-release cysteamine bitartrate capsules)

(b) (4)  
Section 7.3.5 (Submission-Specific Primary Safety Concerns) includes a review of cysteamine-associated CNS events from clinical trials, post-marketing reports, and the medical literature.

### **7.3 Major Safety Results**

#### **7.3.1 Deaths**

No deaths have been reported during clinical trials of Procysbi.

#### **7.3.2 Nonfatal Serious Adverse Events**

Forty-eight serious adverse events (SAEs) occurred in 22 (37.3%) of the 59 patients in the safety dataset (Table 19: Serious Adverse Events in RP103-04 Table 19). Eighteen of these 22 patients (82%) are RP103-03 patients, while 3 (14%) are patients  $\leq 6$  years old. Six events (5 patients) were considered to be possibly related to Procysbi treatment (i.e., adverse reactions) by the Investigator, and this reviewer concurs with these assessments. None of these 6 severe adverse reactions occurred in patients  $\leq 6$  years old. One patient (Subject 09001, RP103-03 patient subgroup) was discontinued from participation in RP103-04 due to the SAE (renal failure), and the event was still unresolved at last assessment. All other events resolved without sequelae. Brief narratives are provided for the serious adverse reactions.

**Table 19: Serious Adverse Events in RP103-04**  
**(Adverse Reactions are Indicated by Boxes around Preferred Terms)**

Subject No./ (Population <sup>1</sup> )	Preferred Term	Severity (Grade)	Outcome
01001 (RP103-03)	Genu Valgum	1	Recovered/Resolved
	Surgery for Genu Valgum	2	Recovered/Resolved
01004 (RP103-03)	Cryptorchism	1	Recovered/Resolved
02010 (RP103-03)	Gastroenteritis	3	Recovered/Resolved
	Gastroenteritis	2	Recovered/Resolved
	Hypokalaemia	2	Recovered/Resolved
	Vomiting	2	Recovered/Resolved
	Anaemia	3	Recovered/Resolved
02011 (RP103-03)	Constipation	3	Recovered/Resolving
	Hypokalaemia	2	Recovered/Resolved
	Appendicitis Perforated	3	Recovered/Resolved
	Vomiting	2	Recovered/Resolved
02109 (RP103-03)	Gastroenteritis	2	Recovered/Resolved
	Vomiting	3	Recovered/Resolved
03004 (RP103-03)	Renal Failure Chronic	2	Recovered/Resolved
	Kidney Transplant Rejection	2	Recovering/Resolved
	Kidney Transplant Rejection	2	Recovering/Resolved
	Kidney Transplant Rejection	3	Recovering/Resolved
	Hypertension	2	Recovered/Resolved

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Table 19 (continued)

Subject No./ (Population )	Preferred Term <sup>2</sup>	Severity (Grade)	Outcome
03007 (≤6 yrs. And RP103-03)	Tonsillar Hypertrophy	2	Recovered/Resolved
03101 (RP103-03)	Gastric Fistula	1	Recovered/Resolved
04302 (RP103-03- 02-014)	Appendicitis	4	Recovered/Resolved
05005 (renal)	Graft Dysfunction	2	Recovering/Resolved
	Abnormal Behavior	3	Recovered/Resolved
06001 (RP103-03)	Appendicitis	2	Recovered/Resolved
06002 (RP103-03)	Knee Deformity	2	Recovered/Resolved
	Knee Deformity	2	Recovered/Resolved
06003 (RP103-03)	Renal Failure	3	Recovered/Resolved
06006 (RP103-03)	Diarrhoea	2	Recovered/Resolved
07002 (RP103-03)	Alcohol Poisoning	2	Recovered/Resolved
	Hypocalcaemia	4	Recovered/Resolved
	Hypocalcaemia	3	Recovered/Resolved
	Pseudoparalysis	3	Recovered/Resolved
	Mental Disorder	1	Recovered/Resolved
	Salpingitis	3	Recovered/Resolved
07003 (RP103-03)	Gastroenteritis	3	Recovered/Resolved
	Gastroenteritis	2	Recovered/Resolved
07004 (RP103-03)	Knee Deformity	2	Recovered/Resolved
	Hyponatraemia	2	Recovered/Resolved
	Hyponatraemia	3	Recovered/Resolved
	Hyponatraemia	2	Recovered/Resolved
07006 (≤6 yrs.)	Otitis Media Chronic	1	Recovered/Resolved
08004 (≤6 yrs.)	Dehydration	3	Recovered/Resolved
08005 (≤6 yrs.)	Dehydration	3	Recovered/Resolved
	Gastroenteritis	3	Recovered/Resolved
09001 (RP103-03)	Renal Failure	3	Discontinued from Study
09002 (RP103-03)	Urethritis	2	Recovered/Resolved
	Knee Deformity	2	Recovered/Resolved

(Source: Adapted from Applicant's Table 53, "Summary of SAEs (Safety Population)", RP103-04 Interim Clinical Study Report page 176/201, NDA 203389, Module 5.3.5.2)



### **Narratives of Serious Adverse Reactions (n=6)**

- **Subject 02010- Vomiting**: 13-year-old male hospitalized for nausea, vomiting, and diarrhea, resulting in dehydration and hypokalemia. In addition to intravenous hydration, the patient's dose of omeprazole was increased.

*This event was considered by the Investigator to be possibly related to Procysbi treatment and is consistent with the known effects of cysteamine. Seven gastrointestinal AEs were reported for this patient—vomiting (n=3), gastroenteritis (n=2), decreased appetite (n=1), diarrhea (n=1). No Procysbi dose reductions were performed.*

- **Subject 02011- Constipation**: 12 year-old female subject (hospitalized for evaluation and treatment of severe abdominal pain of one-month duration. “Dark specks” were noted in gastrostomy tube secretions. The subject underwent a complete bowel cleanout and omeprazole was added to her regimen.

*This event was considered by the Investigator to be possibly related to Procysbi treatment, and constipation has been reported as one of the gastrointestinal effects associated with cysteamine. One additional constipation event was reported for this patient. Other gastrointestinal events with plausible relationship to study drug were abdominal pain (intermittent and not recovered/resolved) and vomiting. Procysbi dose remained unchanged.*

- **Subject 02109- Vomiting**: 7 year-old male hospitalized due to emesis resulting in dehydration.

*This episode of vomiting was considered by the Investigator to be possibly related to Procysbi treatment. (See below)*

- **Subject 02109- Gastroenteritis**: 9 year-old male hospitalized for dehydration due to vomiting (unresponsive to ondansetron) and diarrhea.

*This event was considered by the Investigator to be possibly related to Procysbi treatment. Although this event may be consistent with an acquired infectious gastroenteritis, this patient experienced several other gastrointestinal adverse events during RP103-04—vomiting (n=7) and diarrhea (n=2). The patient's daily dose was increased from 1100 mg/day (1375 mg/m<sup>2</sup>/day) to 1650 mg/day (1833 mg/m<sup>2</sup>/day), exceeding the previous Cystagon daily dose of 1600 mg/day. Most of the gastrointestinal events were reported while the patient was receiving the highest dose of Procysbi. In addition, the patient experienced 2 months of intermittent fatigue following the increase to this dose.*

- **Subject 06006- Chronic Diarrhea**: 11 year-old Caucasian male hospitalized due to chronic diarrhea of 2-3 weeks duration. The patient was experiencing 7 to 10 loose, watery, non-bloody bowel movements per day. No changes to Procysbi treatment were made.

*This event was considered by the Investigator to be possibly related to Procysbi treatment, although the patient's diarrhea reportedly improved following discontinuation of the oral*

*iron supplement.*

- **Subject 09001- Renal failure:** 14-year-old male subject with renal insufficiency. The patient began Procysbi treatment with an estimated glomerular filtration rate (eGFR) of 80 mL/min/1.72 m<sup>2</sup> and creatinine ~0.85 mg/dL. After approximately 1.5 years of treatment, the patient's eGFR was 40 mL/min/1.72 m<sup>2</sup>, and 2 months later, it had declined to mL/min/1.72 m<sup>2</sup>. Compliance with Procysbi treatment was confirmed.

*This event was considered by the Investigator to be possibly related to Procysbi treatment, and study participation was discontinued due to this event. As of the data cutoff date, this event was reported as ongoing/unresolved. Although most cases of renal impairment in patients with cystinosis can be attributed to the underlying disease, this patient experienced a more rapid decline in renal function than expected in a cysteamine-compliant patient with a baseline eGFR of 80 mL/min/1.73 m<sup>2</sup>. During the 20 months of RP103-04 participation, this patient's WBC cystine levels were consistently well within the target range, with a mean (±SD) of 0.29 (±0.22) nmol ½ cystine/mg protein, range 0.05 to 0.67 nmol ½ cystine/mg protein, and no other adverse events were noted which could explain this severe, progressive decline in renal function. Distinguishing possible effects of treatment from the underlying disease is difficult; however, based on the available information, an adverse effect of Procysbi must be strongly considered. This case represents one of XX patients identified by this Reviewer whose renal function declined during RP103-04 more rapidly than would expected based on level of baseline eGFR, though this patient's deterioration was the most marked. A review of these cases can be found in Section 6.1.6 Other Endpoints) since the evolution of GFR was an exploratory efficacy endpoint.*

### 7.3.3 Dropouts and/or Discontinuations

Six patients withdrew from Study RP103-04 after enrollment (Table 20), 5 of which are included in the Safety Database.

**Table 20: Withdrawals from Study RP103-04, in Order by Length of Study Participation (N=6)**

Patient ID	Patient Group	Timing of Withdrawal		Reason for Dropout/ Discontinuation
		Study Day	Study Month	
06007*	≤ 6 years old	---	---	Unable to take study drug
07001	RP103-03	56	1.8	Adverse reaction
02107	RP103-03	103	3.4	Adverse reaction
01006	Transplant	57	1.9	Investigator decision**
02012	RP103-03	585	19.2	Withdrawal of consent
09001	RP103-03	613	20.2	Adverse Reaction/ physician judgment

(Source: Reviewer's table using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

\* Subject 06007 did not receive any doses of Procysbi and is not included in either the PK/PD or safety datasets

\*\* Patient withdrawn at the discretion of the Investigator due to noncompliance discovered during the dose confirmation period

Three patients discontinued treatment and withdrew from study participation due to adverse reactions, all of whom had completed Study RP103-03:

- Subject 02107: intermittent Grade 2 vomiting of approximately two months duration, unsuccessfully treated with ondansetron, and with resolution without sequelae after discontinuation of Procysbi
- Subject 07001: persistent symptoms of decreased appetite and dyspepsia, both grade 1 in severity, of approximately one month duration, unresponsive to treatment (not specified), and with resolution without sequelae following discontinuation of Procysbi
- Subject 09001: development of Grade 3 renal failure (SAE), which at last report, had not resolved; renal failure was considered by the Investigator to be possibly related to treatment with study drug; a more detailed narrative is provided in Section 7.3.2 (Non-Fatal Serious Adverse Events)

Two additional patients were reported to have temporarily discontinued of Procysbi treatment during RP103-04 due to adverse reactions, but both patients resumed Procysbi treatment and remained enrolled in RP103-04.

- Subject 01004 (RP103-03 patient): 11-year-old (at study entry) who experienced intermittent Grade 2 vomiting. During 3 of vomiting episodes, the parents interrupted Procysbi treatment and replaced it with Cystagon, and these treatment interruptions were reported as treatment non-compliance protocol deviations. This patient's Procysbi dose was substantially reduced during RP103-04 participation. The initial daily Procysbi dose was 1550 mg/day (1383 mg/m<sup>2</sup>/day) during Study RP103-03 and was increased to 1900 mg (1727mg/m<sup>2</sup>/day). However, during RP103-04 participation, the daily Procysbi dose was decreased incrementally to a minimum dose of 900 mg/day (750 mg/m<sup>2</sup>/day) at Month 14, followed by an increase to the most recently reported dose of 1050 mg (860 mg/m<sup>2</sup>/day) at Month 19.

*This case is consistent with known gastrointestinal effects of Procysbi, and gastrointestinal side effects frequently improve following dose reduction.*

- Subject 03014 (renal transplant patient): 32-year-old (at study entry) experienced multiple episodes of an "acute pain syndrome" with intermittent Grade 3 pain. The patient discontinued Procysbi approximate 3 weeks after the onset of pain, and this treatment interruption was reported as treatment non-compliance protocol deviation. The patient's initial daily Procysbi dose was 1650 mg (1153 mg/m<sup>2</sup>/day). Following treatment interruption, the patient's daily dose was reduced dramatically to 800 mg/day (547 mg/m<sup>2</sup>/day) and the patient continued RP103-04 participation.

*Ehlers-Danlos-like signs and symptoms in bone and connective tissues, including reports of pain, have been associated with cysteamine treatment. However, the mechanism of this patient's generalized acute pain syndrome is not clear, and this reviewer could not*

*find reports of similar reactions to cysteamine. Nevertheless, this event is likely related to Procysbi treatment, based on the timing of onset of symptoms, association with high Procysbi daily dose relative to previous Cystagon daily dose, and resolution of symptoms with discontinuation of Procysbi.*

### 7.3.4 Significant Adverse Events

The only unexpected adverse reaction in RP103-04 was the case of renal failure in Subject 09001. This event is reviewed in Sections 7.3.2 and 7.3.3.

Two life-threatening adverse events and 31 severe adverse events were reported in 15 patients. Four of these events occurred in 3 patients  $\leq 6$  years old (neither of them life-threatening), and none of them have a causal relationship to Procysbi. For 7 of the older patients, 12 events (9 unique events) had a causal relationship with Procysbi treatment. It is unclear whether the overall lower severity of adverse reactions in patients  $\leq 6$  years old is due to their lower mean daily Procysbi doses compare to RP103-03 patients or an age-related effect.

Narratives for notable adverse reactions can be found in either Section 7.3.2 (Nonfatal Serious Adverse Events) or 7.3.5 (Submission-Specific Primary Safety Concerns).

### 7.3.5 Submission-Specific Primary Safety Concerns

This section reviews (1) the adverse reactions from RP103-04 that are relevant to the Warnings and Precautions in the current Procysbi product labeling and (2) concomitant medications to address Procysbi-related adverse effects, particularly gastrointestinal medications (e.g., gastric acid reducing (GAR) medications, antiemetics).

The current prescribing information for both Procysbi and Cystagon includes the following warnings/precautions:

- Gastrointestinal ulcers and bleeding
- Central nervous system symptoms: seizures, lethargy, somnolence, depression, and encephalopathy
- Severe skin rashes such as erythema multiforme bullosa or toxic epidermal necrolysis
- Ehlers-Danlos-like syndrome with skin and bone lesions that resemble clinical findings of Ehlers-Danlos syndrome, including include molluscoid pseudotumors (purplish hemorrhagic lesions), skin striae, bone lesions (including osteopenia, compression fractures, scoliosis and genu valgum), leg pain, and joint hyperextension
- Pseudotumor cerebri
- Neutropenia
- Elevated transaminases

Of the 396 unique adverse events per patient, 148 events in 51 patients met this reviewer’s criteria for a plausible causal relationship with Procysbi treatment. (See Section 7.1.2) These 148 events were assigned to 7 different SOCs (Table 21). Twenty-four of 51 patients (47%) experienced adverse reactions in more than 1 SOC. Overall, the distribution of adverse reactions across SOCs is consistent with the known safety profile of cysteamine and other Procysbi clinical trials. The frequency of organ system-specific adverse reactions for patients ≤6 years old did not appear to differ substantially from the RP103-03 patients, with the possible exception of fewer neuropsychiatric reactions.

It is important to recognize that all patients with available data from Procysbi clinical trials were previously treated with immediate-release cysteamine bitartrate prior to clinical trial participation. Therefore, the degree of Procysbi’s role in the development of adverse reactions resulting from chronic cysteamine exposure may not be clear.

**Table 21: Frequency of Adverse Reactions by Organ System Classification**

	Patients (n, (%))			Unique Events (n, (%))		
	All (n=59)	RP103-03 (n=40)	≤6 years old (n=13)	All	RP103-03	≤6 years old
Any Organ System	51 (86%)	38 (95%)	10 (77%)	148	110	27
Gastrointestinal	45 (76%)	33 (83%)	10 (77%)	99 (67%)	73 (66%)	21 (78%)
Neuropsychiatric	19 (32%)	16 (40%)	2 (15%)	25 (17%)	19 (17%)	2 (15%)
Skin-related	14 (24%)	10 (25%)	3 (15%)	17 (11%)	12 (11%)	4 (15%)
General	5 (8%)	4 (10%)	0 (0%)	5 (3%)	4 (4%)	0 (0%)
Renal	1 (2%)	1 (3%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Musculoskeletal	1 (2%)	1 (3%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)

(Source: Reviewer’s table using Applicant’s Analysis Datasets, NDA 203389, Module 5.3.5.2)

### **Gastrointestinal Symptoms**

Consistent with the known safety profile of cysteamine, gastrointestinal symptoms comprise the largest group of adverse reactions in RP103-04. Ninety-nine unique gastrointestinal reactions were reported which were considered by this reviewer to be reasonably likely to be due to Procysbi treatment. In addition to the PTs assigned to this SOC by the Applicant, this reviewer classified decreased appetite/anorexia as a gastrointestinal adverse reaction based on previous clinical experience with cysteamine products.

Forty-five clinical trial patients experienced at least 1 gastrointestinal adverse reaction [(mean (±SD) 2.2 (±1.0) unique reactions per patient, range 1 to 5 reactions). The types and rates of specific gastrointestinal adverse reactions are listed in Table 22.

The type and incidence of gastrointestinal adverse reactions is patient age groups similar between the patients ≤6 years old and RP103-03 patients, with the exception of breath odor, for which there were no reported events among the patients ≤6 years old. Whether this is the result

of the lower Procysbi doses in this patient subgroup, a lack of self-reporting in this age group, or a true age-related difference is not known.

Gastrostomy tube failure (i.e., clogging of the gastrostomy tube due to Procysbi administration) is the only adverse reaction from RP103-04 not previously reported with Procysbi use. However, prior to Amendment 5 of RP103-04, Procysbi was administered only as an intact capsule. Therefore, this is the first opportunity to review data with administration of opened Procysbi capsules and use of gastrostomy tubes. The current Procysbi labeling includes specific instructions for administration of opened Procysbi capsules via gastrostomy tube aimed to ensure that the entire dose is administered to the patient and minimize tube obstruction, (b) (4). The administration instructions in the labeling were evaluated during this review cycle, and the labeling recommendations for section of the prescribing information are included in Section 9.2 Labeling Recommendations

**Table 22: Gastrointestinal Adverse Reactions in Study RP103-04**

	All (n=59)	RP103-03 (n=40)	≤6 Years Old (n=13)
Any	45 (76%)	33 (83%)	9 (69%)
Vomiting	35 (59%)	26 (65%)	8 (62%)
Abdominal Pain	14 (24%)	10 (25%)	4 (31%)
Diarrhea	10 (17%)	7 (18%)	3 (23%)
Breath Odor Abnormal/Halitosis	7 (12%)	7 (18%)	0 (0%)
Nausea	7 (12%)	4 (10%)	1 (8%)
Decreased Appetite	5 (8%)	4 (10%)	1 (8%)
GERD/Dyspepsia	4 (7%)	3 (8%)	0 (0%)
Constipation	2 (3%)	1 (3%)	0 (0%)
Gastrostomy Tube Failure*	3 (5%)	1 (3%)	2 (15%)
Abdominal Distention	1 (2%)	0 (0%)	1 (8%)
Dysphagia	1 (2%)	1 (3%)	0 (0%)
Flatulence	1 (2%)	1 (3%)	0 (0%)
Peptic Ulcer	1 (2%)	1 (3%)	0 (0%)

(Source: Reviewer's table using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

### **Concomitant Gastrointestinal Medications**

Table 23 summarizes the use of gastrointestinal medications for all subgroups during RP103-04. By far, the most frequent concomitant gastrointestinal medications were proton pump inhibitors (PPI). PPIs were used by 51% of all RP103-04 patients, including 53% of RP103-03 patients and 69% of patients ≤6 years old. Because cysteamine causes gastric acid hypersecretion [38], and PPIs are the recommended treatment for cysteamine-related gastrointestinal side effects [12,38], this class of medications is frequently used by patients with nephropathic cystinosis, and the rate of PPI use during RP103-04 is consistent with known use in this patient population.

**Table 23: Use of Gastrointestinal Medications during RP103-04**

Medication Class/ Medication*	All (n=59)	RP103-03 (n=40)	≤6 years old (n=13)
<b>Antacids</b>			
<i>Proton pump inhibitors</i>	30 (51%)	21 (53%)	9 (69%)
H <sub>2</sub> receptor antagonists	5 (8%)	3 (8%)	1 (8%)
Charcoal	1 (2%)	1 (3%)	0 (0%)
Alka seltzer	1 (2%)	0 (0%)	0 (0%)
Aluminum/magnesium	1 (2%)	1 (3%)	0 (0%)
Peptobismol	2 (3%)	2 (5%)	0 (0%)
<b>Prokinetics</b>			
Metoclopramide	4 (7%)	3 (8%)	1 (8%)
Erythromycin	1 (2%)	1 (3%)	0 (0%)
Domperidone	3 (5%)	1 (3%)	2 (15%)
<b>Antiemetics</b>			
<i>Ondansetron</i>	16 (27%)	11 (28%)	5 (38%)
Antihistamines	2 (3%)	2 (5%)	0 (0%)
Promethazine	2 (3%)	1 (3%)	1 (8%)
<b>Laxatives/stool softeners</b>			
<b>Anti-diarrheals</b>	6 (10%)	4 (10%)	1 (8%)
<b>Probiotics</b>	6 (10%)	2 (5%)	4 (31%)
<b>Anti-spasmodics</b>	3 (5%)	0 (0%)	1 (8%)
<b>Appetite Stimulant (Megace)</b>	5 (8%)	4 (10%)	1 (8%)
<b>Pancreatic Enzymes</b>	1 (2%)	1 (3%)	0 (0%)
<b>Halitosis treatment</b>	2 (3%)	1 (3%)	0 (0%)
Chlorophyll	2 (3%)	2 (5%)	0 (0%)
Vitamin B12	1 (2%)	1 (3%)	0 (0%)
Zinc	1 (2%)	1 (3%)	0 (0%)
Parsley/Sunflower oils	1 (2%)	1 (3%)	0 (0%)

(Source: Reviewer's table using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

\* If only one medication in a medication class was identified as a concomitant medication in RP103-04, the medication name, rather than the medication class is listed

Prior to Procysbi treatment in RP103-03, patients were required to discontinue all GAR medications, and use of these medications during Procysbi treatment was restricted to patients with "intolerable" symptoms. During the RP103-03, 5 of 39 patients (13%) received GAR medications (predominantly PPIs), while 56% of patients in RP103-04 (33 of 59) used at least 1 GAR medication during study participation (55% of RP103-03 patients and 77% of patients ≤6 years old).

Due to the high rate of use of gastrointestinal medications, particularly chronic use, during

RP103-04, no conclusions regarding the improvement or resolution of gastrointestinal adverse reactions could be drawn. (See Section 7.5.2, Time Dependency for Adverse Events).

**Neuropsychiatric Adverse Reactions**

Adverse reactions from the central nervous system (CNS) and psychiatric SOCs were combined and are presented in Table 24. Consistent with the current product labeling, headaches were the most common of these adverse reactions. In the patients ≤6 years old, no other neuropsychiatric reactions were reported. Again, it is unclear whether this difference between groups is due to differences in dose level or represents a true age-related difference in safety profile.

**Table 24: Neuropsychiatric Adverse Reactions in Study RP103-04**

	All (n=59)	RP103-03 (n=40)	≤6 Years Old (n=13)
Any	19 (32%)	16 (40%)	2 (15%)
Headache	17 (29%)	14 (37%)	2 (15%)
Weakness	2 (3%)	1 (3%)	0 (0%)
Diminished reflexes	1 (2%)	1 (3%)	0 (0%)
Dizziness	1 (2%)	1 (3%)	0 (0%)
Forgetfulness	1 (2%)	0 (0%)	0 (0%)
Depression	2 (3%)	1 (3%)	0 (0%)
Lethargy	1 (2%)	1 (3%)	0 (0%)

(Source: Reviewer’s table using Applicant’s Analysis Datasets, NDA 203389, Module 5.3.5.2)

Use of medications for psychiatric indications among RP103-04 patients included stimulants (n=2; both RP103-03 patients), antidepressants (n=3; 1 RP103-03 patient and 2 transplant patients), antipsychotics (n=1; RP103-03 patient), and oxcarbazepine (n=1; RP103-03 patient).

Although headache was the only adverse reaction experienced by >5% of RP103-03 patients, a more comprehensive discussion of the neuropsychiatric reactions experienced by these patients is important (b) (4)

Section 5 of the Procybsi label current states the following:

“Central Nervous System (CNS) symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with immediate-release cysteamine. Neurological complications have also been described in some patients with cystinosis who have not been treated with cysteamine.”

(b) (4)



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Although disease-related neurologic manifestations are recognized sequelae of long-standing nephropathic cystinosis [41], CNS reactions have also been reported as a treatment-related complication.[45-47] Symptoms of encephalopathy, such as confusion, memory difficulties, psychiatric manifestations, and lethargy, as well as gait disturbances, muscle weakness, tremor, attention difficulties have been reported as both disease-related and treatment-related effects. However, events attributed to cysteamine use typically have a more rapid onset, resolve or improve with cysteamine dose reduction/discontinuation, occur in patients of all ages, and are less likely to be associated with radiologic abnormalities.[46] They are also more likely to occur during treatment initiation, with the use of high doses, and during rapid dose escalation. On the other hand, the encephalopathy of nephropathic cystinosis is generally a late complication with an insidious onset of irreversible gross neurological abnormalities after the second decade of life. [20]

In the original cysteamine clinical trials, a dose-related encephalopathy was described. Although the possibility of cystinosis-related CNS effects was considered, the NDA clinical review for Cystagon reports that CNS adverse reactions (seizure, memory loss, nightmares, depression, jitteriness, nervousness, and hallucinations) occurred with higher dosages, were reversible with treatment discontinuation, and often did not recur upon resumption of treatment at a lower cysteamine dose. [FDA Action Package for NDA 20392, clinical reviews by Lilia Talarico, MD and Robert J. Temple, MD]

Between 2004 and 2014, at least 10 cases of CNS events attributed to Cystagon, occurring in patients aged 5 to 30 years old, were reported through the FDA Adverse Event Reporting System (FAERS). Reported symptoms included amnesia, encephalopathy, convulsion/epilepsy, cerebral ischemia, gait disturbance, confusion, asthenia, abnormal behavior, weakness, tremor, dementia, depression, attention disturbance, memory impairment, emotional disorder, hallucination, and nervousness. Some case reports were reviewed in detail, while others were identified using a publicly-available database which collates de-identified FAERS data obtained from quarterly FAERS reports (www.pharmapendium.com). Because a formal review of all complete FAERS reports was not performed, this information cannot be used to make independent conclusions regarding the neurologic effects of cysteamine bitartrate. Since most published reports of CNS reactions with cysteamine pre-date the approval of Cystagon and occurred in patients treated with unapproved cysteamine formulations and/or doses, this reviewer used this information to complement literature search results by providing evidence of recent CNS reactions in patients treated with cysteamine bitartrate. It is important to note that although medications doses were reported inconsistently, among these cases were patients who were reported as receiving doses within the recommended range.

Although serious CNS reactions have not been reported during Procysbi clinical trials or in the post-marketing period, CNS symptoms comprised the second most common group of adverse reactions in RP103-04. CNS symptoms which have been attributed to Procysbi treatment include headaches, dizziness, and (b) (4). Other CNS reactions from RP103-04 considered by this reviewer to be reasonably likely to be due to or exacerbated by Procysbi include lethargy, forgetfulness, depression, and (b) (4). These events are consistent with the current warnings

in the prescribing information.

As discussed in 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations), the doses evaluated in Procysbi clinical trials were frequently lower than recommended doses. In addition, no Procysbi safety data are available for cysteamine-naïve patients. Because these events may be more likely to occur during treatment initiation, the safety profile of Procysbi is incomplete without data in this patient population. However, as a drug approved under the 505(b)(2) regulatory pathway, safety data from its listed drug can be relied upon to make up for these inadequacies, and the label needs to include the same safety information as the listed drug.

Based on review of the available data, this reviewer considers the safety profile of Procysbi to be similar to that of other cysteamine formulations.

### **Other Adverse Reactions**

Dermatological reactions are shown in Table 25. Consistent with the known side effect profile of cysteamine, abnormal skin/sweat/body odor was the most common of skin-related adverse reactions. Rashes which this reviewer considered reasonably likely to be due to Procysbi also occurred in >10% of patients. Although none of these rashes could be categorized as any of the severe skin reactions which are included in the labelled warning (i.e., erythema multiforme bullosa and toxic epidermal necrolysis), urticarial rashes are suggestive of hypersensitivity reactions, which have been described as a significant adverse reactions to Procysbi and other cysteamine formulations.

Also notable is the report of “excess skin development”, occurring in Subject 09003 (RP103-03 patient). This likely represents an Ehlers-Danlos-like reaction, a labelled warning not previously reported in patients treated with Procysbi. The outcome of the event was not recorded at the time of the data cutoff for the Interim CSR. This event was reported in a 23-year-old male with a history of a molluscoid pseudotumor on the left elbow since May 2010. Molluscoid pseudotumors or angioendotheliomatosis, specifically on the elbows, represent a recognized Ehlers-Danlos-like manifestation in cysteamine-treated patients due to direct cysteamine effects on collagen cross-linking and stimulation of human dermal microvascular cell survival/proliferation.[45,53] In this patient, the onset of the molluscoid pseudotumor pre-dated Procysbi treatment; however, the patient had been treated with Cystagon since his diagnosis of nephropathic cystinosis at 1 year of age. Lower extremity pain was also reported among this patient’s adverse events. Because musculoskeletal pain is a common disease-related manifestation, none of these events were classified as treatment-related. However, lower extremity pain is also listed among the Ehlers-Danlos-like symptoms in the label.

**Table 25: Skin-related Adverse Reactions**

	All (n=59)	RP103-03 (n=40)	≤6 Years Old (n=13)
<b>Any</b>	14 (24%)	10 (25%)	3 (23%)
Skin/sweat odor abnormal; bromhidrosis	7 (12%)	4 (10%)	2 (15%)
Rash (all)	7 (12%)	5 (13%)	2 (15%)
Urticaria	2 (3%)	2 (5%)	0 (0%)
Skin hypopigmentation	1 (2%)	0 (0%)	1 (8%)
Blisters on lower extremities	1 (2%)	0 (0%)	1 (8%)
Red plaques	1 (2%)	1 (0%)	0 (0%)
Excess skin on elbows	1 (2%)	1 (3%)	0 (0%)
Alopecia areata	1 (2%)	1 (3%)	0 (0%)
Hot flush	1 (2%)	1 (3%)	0 (0%)

(Source: Reviewer's table using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

The adverse reactions that do not belong to one of the previously discussed SOC's are listed in Table 26. Of the reactions not previously discussed in this review, the report of exostosis is considered to be a notable reaction by this reviewer. (The cases of acute pain syndrome and renal impairment are detailed in Sections 7.3.5 and 7.3.2, respectively.)

**Table 26: Adverse Reactions from other SOC's**

	All (n=59)	RP103-03 (n=40)	≤6 Years Old (n=13)
<b>General</b>			
Fatigue/asthenia	4 (7%)	4 (10%)	0 (0%)
Acute pain syndrome	1 (2%)	0 (0%)	0 (0%)
<b>Renal</b>			
Renal Impairment	1 (2%)	1 (3%)	0 (0%)
<b>Musculoskeletal</b>			
Exostosis	1 (2%)	1 (3%)	0 (0%)

(Source: Reviewer's table using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

A single case of exostosis was reported in Subject 09002, an RP103-03 patient. Exostosis is defined as a benign outgrowth of cartilaginous tissue on a bone. Like the case of excess skin, this connective tissue abnormality may represent a finding on the spectrum of the Ehler-Danlos-like syndrome reported with cysteamine treatment. Therefore, these 2 cases may represent the first reports of this type of reaction with Procysbi. Like Subject 09003 who developed excess skin on his elbows, this patient also complained of lower extremity pain. Genu valgum was also reported as an adverse event in this patient. Although genu valgum is also listed as one of the possible Ehler-Danlos-like symptoms due to Procysbi, this event is more likely a skeletal complication of long-standing Fanconi syndrome; therefore, this event, which occurred in 5 clinical trial patients, was not considered an adverse reaction. Nevertheless, multiple reports of potential Ehler-Danlos-like symptoms were reported in the same patient.

Neutropenia is one of the warnings included in the Procysbi labeling. One patient (03004) experienced adverse events of neutropenia and neutropenia during RP103-04. Although these AEs were classified as “possibly related” to Procysbi, this reviewer did not consider either of these events to be related to Procysbi treatment since they occurred following initiation of a combination of post-transplant medications more likely than Procysbi to cause these hematologic abnormalities.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Gastrointestinal adverse reactions comprised the most common adverse reactions in RP103-04, consistent with the known safety profile of Procysbi and other cysteamine products (Table 26). The gastrointestinal symptoms occurring in >5 % of patients in RP103-04 are the same as those reported in >5% of patients other cysteamine clinical trials—vomiting, nausea, abdominal pain, anorexia/loss of appetite, and diarrhea.

**Table 27: Comparison of Most Common Adverse Reactions between Cystagon and Procysbi Treatment Arms of Study RP103-03 (Table 2 in Currently Approved Procysbi Label)**

Adverse Reaction	Immediate-release cysteamine	PROCYSBI
	(n = 41) %	(n = 43) %
Vomiting/emesis	12	19
Nausea	7	16
Abdominal pain/discomfort	0	14
Headache	0	9
Dizziness	0	5
Anorexia/loss of appetite	5	2

(Source: Current Procysbi label (approved April 30, 2013) available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

The most common non-gastrointestinal adverse reactions observed in >5% RP103-04 were noted in >5% of other clinical trial patients—breath odor, skin odor, fatigue, headache, and rash.

In general, symptoms in patients ≤6 years old are similar to the rest of the clinical trial population. No new safety concerns were identified in the patient ≤6 years old, with the exception of gastrostomy tube failure. The identification of his treatment complication comes only after the new enrollment of patients who cannot take intact Procysbi capsules, including patients with gastrostomy tubes. This mechanical complication, rather than a medical complication, was addressed during labeling discussions of administration procedures.

### 7.4.2 Laboratory Findings

The majority of laboratory abnormalities in RP103-04 most likely occurred as a result of patients’ underlying disease (i.e., Fanconi syndrome/renal tubular acidosis, chronic renal

insufficiency); chronic comorbid conditions, including medications for these comorbid conditions (e.g., kidney transplant, renal allograft rejection); and acute comorbid events (e.g., viral gastroenteritis, appendicitis). In the opinion of this reviewer, this includes all of the abnormal hematology and urinalysis study results.

Similarly, the majority of blood chemistry abnormalities also have a likely etiology other than Procysbi toxicity. In some cases, blood chemistry abnormalities were secondary to Procysbi adverse reactions, such as vomiting leading to dehydration with associated laboratory abnormalities such as blood urea nitrogen, serum creatinine, serum bicarbonate, and serum electrolytes. However, these abnormalities are not direct effects of Procysbi treatment (i.e., nephrotoxicity). Only a few laboratory abnormalities were considered by this reviewer to be reasonably likely to represent adverse reactions to Procysbi treatment. Table 28 shows the blood chemistry abnormalities which the Applicant categorized as TEAEs.

**Table 28: Blood Chemistry Abnormalities Reported as Treatment-Emergent Adverse Events (TEAEs) in RP103-04**

Subject Number	Preferred Term	Severity (Grade)	Subpopulation
01004	Hypophosphataemia	1	RP103-03
01007	Blood creatinine ↑	1	Renal transplant
02010	BUN ↑	1	RP103-03
	Blood creatinine ↑	1	
	Hypokalaemia	2	
02011	Hypokalaemia	2	RP103-03
03006	Hypoglycaemia	1	RP103-03
03101	Hypokalaemia x 2	2 and 1	RP103-03
04003	Hypernatraemia	1	≤6 years of age
	Hypomagnesaemia	1	
	Hypophosphataemia	1	
04302 (RP103-03-02-014)	Blood creatinine ↑	1	RP103-03
	Hyperglycaemia	1	
	Hypokalaemia	1	
05005	Blood creatinine ↑	2	Renal transplant
07002	Hypocalcaemia x 2	4 and 3	RP103-03
07004	Hypokalaemia	1	RP103-03
	Hyponatraemia x 3	2, 3 and 2	
09001	Blood creatinine ↑	2	RP103-03
09003	Hyperglycaemia	1	RP103-03
	Hypophosphataemia	2	

(Source: Adapted from Applicant's Table 55, "Blood Chemistry Abnormalities Reported as TEAEs (Safety Population)", RP103-04 Interim Clinical Study Report page 181/201, NDA 203389, Module 5.3.5.2)

Of the events listed in Table 28, only the increased serum creatinine in Subject 09001 is considered by this reviewer to represent a Procysbi adverse reaction. Although reported as a

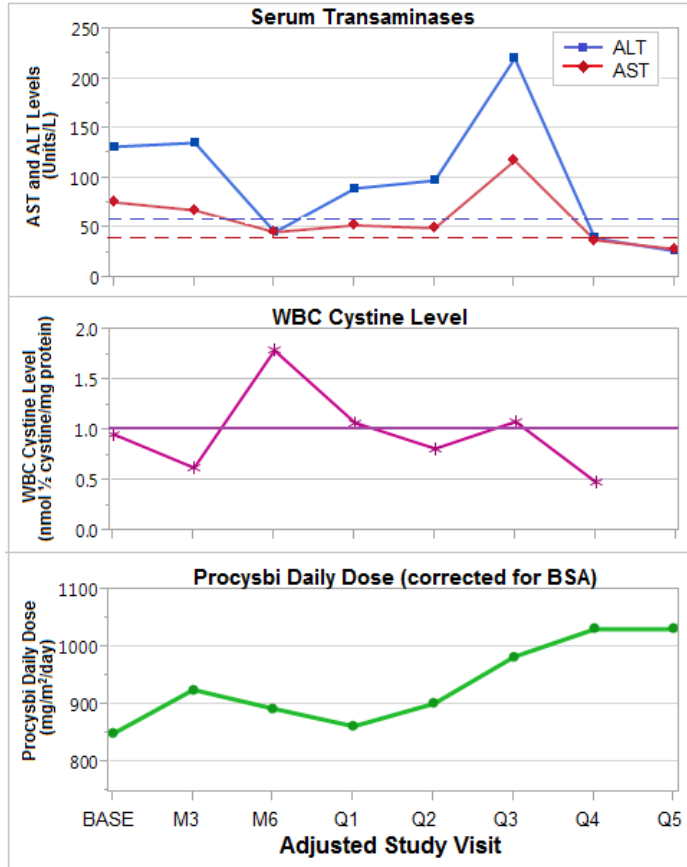
separate event, this AE is likely related to the renal failure (grade 3) experienced by this patient, which led to withdrawal from the clinical trial (See Section 7.3.2).

As indicated by the Applicant, serum creatinine levels, and corresponding estimated glomerular filtration rates (eGFR), tended to fluctuate over the study period. Transient elevations in creatinine levels occurred in several patients in association with dehydration, as expected for this patient population with uncontrolled renal fluid and electrolyte losses due to Fanconi syndrome and variable degree of underlying renal insufficiency. The occurrence of these events in a small patient population interfered with assessments of renal function for both safety and efficacy evaluations.

Although no cases of abnormal transaminase levels were reported by the Applicant, this reviewer identified 6 patients with at least one elevated transaminase level (Subjects 02002, 02013, 03004, 03011, 03013, 08004), of which 2 had elevations in both alanine aminotransferase (ALT) and aspartate aminotransferase (AST), Subjects 02002 and 03011. Only the transaminase abnormalities in Subject 03011 are considered to be clinically significant by this reviewer.

Subject 03011, a patient in the  $\leq 6$  year old subgroup, had a baseline ALT level of 132 units/L and AST level of 76 units/L (2.3 and 1.9 times the upper limit of normal, respectively). (Note: study eligibility criteria specified exclusion of patients with ALT and/or AST  $>1.5$  times the upper limit of normal within 6 months of study participation.) Although elevated transaminases are listed as a warning in the Procysbi product labeling, this case seems more likely related to the patient's underlying disease because levels improved with dose escalation, along with WBC and cystine levels (Figure 31). However, because this patient was receiving Cystagon prior to treatment with Procysbi, the possibility of cysteamine-induced toxicity cannot be completely ruled out.

**Figure 31: Serum Transaminase levels by Adjusted Study Visit with Corresponding WBC Cystine Levels and Procysbi Daily Dose**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)  
 Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase;  
 Base, baseline; BSA, body surface area

### 7.4.3 Vital Signs

No clinically significant vital sign abnormalities were noted during this review.

### 7.4.4 Electrocardiograms (ECGs)

Electrocardiogram (ECG) abnormalities were reported for 5 patients in Study RP103-04 (Table 29).

**Table 29: Electrocardiogram (ECG) Abnormalities in RP103-04**

Subject Number	Study Visit	ECG Abnormality
01007	Quarterly 4	Right ventricular hypertrophy
	Quarterly 5	Right ventricular hypertrophy
02012	Month 1	Left ventricular hypertrophy
	Month 2	Left ventricular hypertrophy; prolonged QT interval
02109	Month 2	First degree AV block; probable left ventricular hypertrophy
	Month 5	Repolarization abnormality that suggests left ventricular hypertrophy
03004	Month 3	Probable right ventricular hypertrophy; left ventricular hypertrophy with secondary repolarization abnormalities; borderline prolonged QT interval
04003	Day 1	Left ventricular hypertrophy, possible right ventricular hypertrophy and early repolarization
	Quarterly 2	Prolonged PR interval and nonspecific T-wave abnormality

(Source: Applicant's Table 56, "Summary of Clinically Significant ECG Evaluations (Safety Population)", RP103-04 Interim Clinical Study Report page 183/201, NDA 203389, Module 5.3.5.2)

Per protocol, all Study Visits included an ECG. Based on the information presented in Table 29, only Subject 03007 (RP103-03 patient) had a finding which may be persistent (the Quarterly 5 visit was Subject 03007's last Study Visit prior to data cutoff), and the nature of this patient's ECG abnormalities are unlikely to be due to Procysbi treatment. Right or left ventricular hypertrophy was common to all 5 subjects who have developed clinically significant ECG abnormalities, which is consistent with the assessment that these abnormalities are likely not treatment related.

#### 7.4.5 Special Safety Studies/Clinical Trials

None

#### 7.4.6 Immunogenicity

Not applicable.

### 7.5 Other Safety Explorations

None

#### 7.5.1 Dose Dependency for Adverse Events

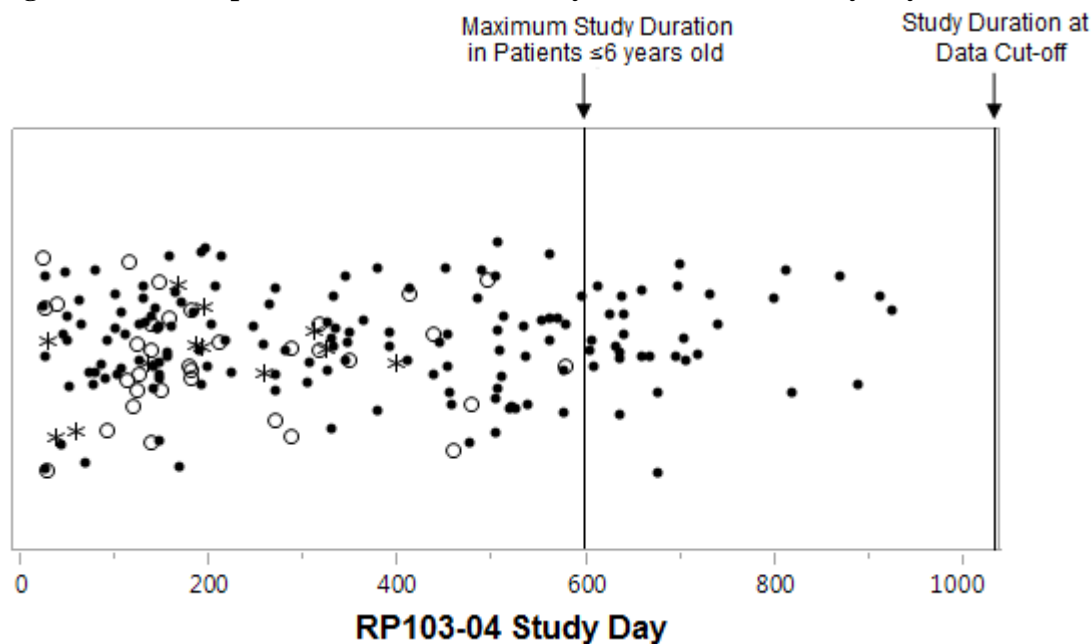
The absence of standardized dosing procedures preclude formal dose-related safety analyses.



### 7.5.2 Time Dependency for Adverse Events

In the scatterplot of adverse reactions by RP103-04 study day of onset (Figure 32), adverse reactions appear to be well distributed across study time points. No time-dependency pattern can be determined, particularly when taking into consideration the withdrawal of 2 patients with recurrent adverse reactions, the variability in patient enrollment date, and the initiation of medications to treat gastrointestinal side effects.

**Figure 32: Scatterplot of Adverse Reactions by Time of Onset (Study Day)**



(Source: Reviewer's figure using Applicant's Analysis Datasets, NDA 203389, Module 5.3.5.2)

### 7.5.3 Drug-Demographic Interactions

Not assessed

### 7.5.4 Drug-Disease Interactions

Not assessed

### 7.5.5 Drug-Drug Interactions

None evaluated.

### 7.6 Additional Safety Evaluations

None

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### **7.6.1 Human Carcinogenicity**

Not assessed

### **7.6.2 Human Reproduction and Pregnancy Data**

Not assessed

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

No adverse effects on growth were observed during Procysbi treatment, though assessments are confounded by the concomitant use of growth hormone in 37% (20/54) of the pediatric clinical trial patients. Although not pre-specified as a clinical trial endpoint, analyses of the evolution of growth (Z-score) during study participation were included among the efficacy assessments in the RP103-04 Interim CSR. The reader is referred to Section 6.1.6 (Other Endpoints) for a summary of these data.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

There has been 1 postmarketing report of accidental overdose with this medication—the patient took twice the prescribed dose and experience nausea and vomiting without sequelae. This product has a low potential for drug abuse. This drug is not associated with withdrawal or rebound effects.

### **7.7 Additional Submissions / Safety Issues**

None

## **8 Postmarketing Experience**

All 15-day expedited reports from FAERS (FDA Adverse Event Reporting System) between July 2013 and August 2015 submitted under NDA 203389 and Procysbi Periodic Adverse Drug Experience Reports covering the period of July 2013 to April 2015 were reviewed.

Most reported events are consistent with known adverse reactions to Procysbi. Gastrointestinal symptoms consistently representing the most commonly reported events. Other more frequently reported events include worsening of skin odor, fatigue, skin rashes, and headaches.

Among the unexpected events, the following groups of events were considered notable by this reviewer. Cases with other clear etiology were excluded. Because of the nature of post-marketing reports, the number of unique cases is difficult to establish.

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- Musculoskeletal pain: includes the verbatim terms of bone pain, arthralgia, joint pain, musculoskeletal pain, pain in extremity, jaw pain, back pain, hip pain knee pain, sore legs, myalgia

*These were notable due to the relatively high frequency of these reports with onset following initiation of Procysbi. Similar symptoms were common during RP103-04, but none of these adverse events were considered to be related to Procysbi treatment, with the exception of one case of recurrent generalized acute pain syndrome. Musculoskeletal pain is common in patients with nephropathic cystinosis due to electrolyte and bone effects of the underlying disease. Therefore, despite the temporal relationship of these events with Procysbi treatment, it is not possible to establish a relationship between these events and Procysbi.*

- Neuropsychiatric and neuromuscular symptoms: psychosis, depressed mood, moodiness, depression, anger, irritability, aggression, restlessness, insomnia, blurry vision, dysgeusia, dysstasia, disorientation, behavior changes, somnolence, cerebrovascular accident, unilateral blindness, nerve pain, numbness, muscle twitching, muscle spasms, muscle weakness

*These events are consistent with the warnings/precautions of cysteamine bitartrate including in the product labeling. In addition, long-standing nephropathic cystinosis is associated with the development of central nervous system and myopathic symptoms. Distinguishing between disease-related and treatment-related effects in these patients is challenging. However the temporal relationship of these events with initiation or dose escalation of Procysbi is suggestive of drug toxicity risks and indicates that the risk profile of Procysbi is similar to other cysteamine formulations.*

- Renal impairment/disease: increased creatinine, kidney transplant performed, advancement/progression of disease, toxic nephropathy

*Several reports of renal failure (without concomitant dehydration) or transplant occurring following Procysbi initiation were submitted, but patients all had pre-existing chronic renal failure. Therefore, the contribution of Procysbi to the deterioration in renal function cannot be determined.*

Gastrostomy tube occlusion

*Comment: At least 17 cases of gastrostomy tube complications due to Procysbi administration were submitted. This emphasizes the importance of reviewing the administration procedures for patients receiving Procysbi via gastrostomy tube.*

The following 7 narratives represent cases of serious, unexpected events which were reviewed in detail by this reviewer:

- Death due to progression of melanoma: patient's melanoma was diagnosed before initiation of Procysbi, but fatal progression occurred after starting Procysbi

*Comment: This reviewer concurs with the Applicant's assessment that it is unlikely that Procysbi contributed to the fatal progression of the malignant melanoma. However, the*

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*temporal relationship between Procysbi and the progression of melanoma was noted.*

- Worsening of pre-existing muscle weakness: report by parent of a 22-year-old male with worsening of underlying muscle weakness after switching from Cystagon to Procysbi; new bi-pap requirement; Procysbi dose at the time of report was 3300 mg/day (1250 mg every 12 hours), and prior Cystagon dose was 2400mg/day (600 mg every 6 hours)

*Comment: Myopathy is a known complication of nephropathic cystinosis, but the association of symptom worsening with increased doses of cysteamine bitartrate is concerning suggests a possible causal role of Procysbi in this patient's exacerbation of symptoms.*

- Dysstasia (inability to stand) and disorientation: report by the husband of a 32-year-old female patient who experienced a 45-second episode of dysstasia and disorientation following dose escalation of Procysbi, 1 month after switching from Cystagon to Procysbi; 4 hours after her morning Procysbi dose (daily dose 1800mg/day, 900 mg every 12 hours), the patient fell, experienced loss feeling in her legs, and muscle twitching. The event resolved and on follow-up inquiry, no additional neurological symptoms occurred. Medical history included renal transplantation 13 years ago, hypothyroidism. Treatment with Procysbi was continued.

*Disease-related neurologic abnormalities are associated with long-standing nephropathic cystinosis. However, the association of this event with the initiation of Procysbi and the timing of this event corresponding to the  $T_{max}$  of Procysbi, suggest that this represents a treatment-related event.*

- Strokes/broken bones: report from male patient (age unknown, was attending college) who experienced two strokes and multiple broken bones after starting Procysbi; dose and indication, medical history and concomitant medications not reported; outcome is unknown as the patient refused to provide follow-up

*Insufficient information was provided to assess this event, but bone lesions and strokes (due to proliferative vascular changes) have both been reported as part of the Ehlers-Danlos-like syndrome associated with cysteamine treatment. In addition, the suggested temporal relationship of these events with Procysbi raises concerns. However, the paucity of information provided precludes any assessments.*

- Psychotic episode: report from the father of a 9-year-old female patient who was hospitalized due to a psychotic episode approximately one month after starting Procysbi for nephropathic cystinosis; the patient was diagnosed with autism with aggression a few months prior to this episode, but the father reported that the patient's behavior became moodier, angrier, more irritable, and "not quite herself" after starting Procysbi, and began having behavioral issues and psychotic episodes at school. Concurrent medications were not reported. At the time of reporting, Procysbi was discontinued, but the case outcome is unknown.

*The patient's pre-existing condition of autism with aggression suggests an etiology other than Procysbi. However, the worsening of symptoms, including new onset of psychotic*

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*episodes and school behavioral problems, corresponding with the initiation of Procysbi, makes a drug-related effect plausible.*

- Unilateral blindness: report by a 24-year-old male patient who developed complete blindness in the left eye and “unspecified problems” in the right eye associated with eye pain and increased intraocular pressure approximately 9 months after starting Procysbi. Symptoms began during dose titration. Initial Procysbi dosage was 375 mg twice daily, and symptoms began 5 months later (dose was 600 mg twice daily). Dosage was 675 mg twice daily at the time of the report. The patient also reported symptoms of drowsiness, stomach cramps, nerve pain, dry mouth, and numbness in right foot, arm and hand. The patient was receiving peritoneal dialysis. No concomitant meds reported. Therapy with PROCYSBI® was ongoing.

*This reviewer concurs with the Applicant’s assessment that a diagnosis of benign intracranial hypertension cannot be excluded. While there have been reports of benign intracranial hypertension in patients with cystinosis treated with immediate-release cysteamine bitartrate, this would represent the first report in a Procysbi-treated patient. Benign intracranial hypertension is listed among the warnings/precautions in the Procysbi and Cystagon prescribing information. However, a causal relationship between cysteamine and benign intracranial hypertension has not been established, and may represent a disease-related complication (proposed mechanism of chronic meningeal cystine crystal deposition).[54] Nevertheless, a causal relationship with Procysbi cannot be ruled out because onset of this event was coincident with the initiation of treatment and dose escalation of Procysbi.*

- Membranous nephropathy: report from a health care professional regarding a pediatric patient of unknown age and gender (but specified as a child) who experienced membranous nephropathy while receiving Procysbi at an unknown dose and for an unknown indication. No medical history or concomitant medications were reported. Past medications included Cystagon. The overall outcome of the case and action taken with Procysbi was unknown.

*As noted by the Applicant, there have been no previous reports of glomerulonephritis or nephrotic syndrome with Procysbi and is a recognized risk of cysteamine treatment, but a causal relationship between Procysbi treatment and this case of membranous nephropathy cannot be ruled out. Of note, penicillamine, another thiol agent with structural similarities to cysteamine, is recognized as a cause of glomerulopathies including membranous nephropathy.[55-57]*

After careful review of postmarketing reports, the reviewer considers this information supportive of the overall conclusion that the safety profile of Procysbi is similar to other cysteamine products and is consistent with the updated safety information in the product labeling. Although postmarketing reports of renal events have been submitted for both Procysbi and Cystagon, there is insufficient information to establish a relationship between these events and cysteamine treatment due to the advanced nature of the underlying renal disease and/or presence of comorbidities including transplant rejection or transplant immunosuppression, which preclude

assessments of causality.

In conclusion, this reviewer does not recommend any labeling changes based on this information and feels that ongoing post-marketing surveillance is warranted to monitor for previously unidentified adverse effects on bone and renal function.

## 9 Appendices

### 9.1 Literature Review/References

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## 9.2 Labeling Recommendations

Key changes to the labeling agreed upon during labeling negotiations are summarized below.

### Indication

- Expanded the indication statement to include pediatric patients 2 years and older, and “management” was changed to “treatment” to read:  
“Procysbi is indicated for the treatment of nephropathic cystinosis in adults and children ages 2 years and older.”

### Dosage and Administration

- Reorganized the information in this section under 4 subsections: “Dosage”, “Dose Titration”, “Laboratory Monitoring”, and “Administration”
- Divided the “Dosage” subsection into 3 smaller subsections under the subheadings of “Starting Dosage in Cysteamine-Naïve Patients”, “Maintenance Dosage in Cysteamine-Naïve Patients” and “Switching Patients from Immediate-Release Cysteamine Bitartrate Capsules” to clarify dosing instructions based on patients’ cysteamine treatment status prior to starting Procysbi.
- Specified that the recommended Procysbi starting daily dose for patients switching from immediate-release cysteamine bitartrate is equal to the patient’s previous total daily dose of immediate-release cysteamine bitartrate; (b) (4)

(b) (4)

- Revised the table for weight-based maintenance dosing to include the number of Procysbi capsules needed.
- Added a separate table with recommended weight-based starting dosages (1/6 to 1/4 of maintenance dosage) and number of Procysbi tablets needed
- Eliminated recommendations to check cysteamine concentration under laboratory monitoring and instructions to use cysteamine concentration to guide Procysbi dose titration if WBC cystine levels are not available. (See Section 6.1.5 for relevant analyses and discussion).
- As proposed by the Applicant, revised the timing of WBC cystine level collection to reflect that the level should be obtained 12 hours after the previous dose (immediately prior to the administration of the next dose), (b) (4). As shown in Figure 34 (Appendix, Section 9.4.2), changing the recommended PD assessment time point should have minimal effect on WBC cystine levels.
- Revised and organized administration instructions for patients taking intact Procysbi capsules, including clarification of recommended liquids for administration and fasting procedures, and addition of instructions to administer Procysbi at least 1 hour before or 1 hour after bicarbonate- or carbonate-containing medications.
- Revised administration instructions for patients taking open Procysbi capsules, based on input from Patient Labeling, to provide detailed procedures for opening capsules, mixing capsule contents with foods or liquids, and administration via gastrostomy tube

### Contraindications

- Limited existing contraindication to those patients with a “serious” (i.e., anaphylactic) hypersensitivity reaction to penicillamine “or cysteamine”

### Warnings and Precautions

(b) (4)

### Adverse Reactions

- Revised the “Clinical Trials Experience with Procysbi” subsection to only include adverse reaction data from Studies RP103-03 and RP103-04; (b) (4)

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- Modified the list of most common reactions to be consistent with all clinical trial patients, including patients ages 2 to 6 years old
- Deleted (b) (4)
- Removed (b) (4), and relocated appropriate information under the subheading of “Clinical Trials Experience with Procysbi”
- Reorganized adverse reactions in the Postmarketing Experience subsection by organ system

### Drug Interactions

- Created a subheading for the information currently included in this section entitled “Other Medications Used for the Maintenance for the Management of Fanconi Syndrome”
- Included two new interactions under the subheadings of “Drugs that Increase Gastric pH” (b) (4) and “Use with Alcohol” (based on alcohol dumping studies previously reviewed as part of the original NDA, see Figure 37 in the Appendix, Section 9.4.2).
- Moved in vitro information to Section 12.3 Clinical Pharmacology.

### Use in Specific Population

- Revised Subsections 8.1 (Pregnancy) and 8.2 (Lactation) to be consistent with the format in the Pregnancy and Lactation Labeling Rule (PLLR) published on December 4, 2014 (“Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling”); for details, see DPMH consultation review by Dr. Leyla Sahin, dated July 9, 2015
- Revised Subsection 8.4 to reflect that the safety and effectiveness of Procysbi have been established in pediatric patients 2 years and older.

(b) (4)

### Overdosage

- Revised this information to include information from available cases of overdose with any of the cysteamine oral formulations
- Included instructions for management of Procysbi overdosage

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### Clinical Pharmacology

- Revised the “Pharmacokinetics” subsection to follow the format recommendations found in the Clinical Pharmacology labeling guidance.
- Added a subsection on “Omeprazole” to describe the impact of concomitant proton pump inhibitor administration on the pharmacokinetics of Procysbi (see Section 4.4.3)

### Clinical Studies

- Revised the “Clinical Trials with Procysbi” subsection to only include data from Studies RP103-03 and RP103-04. (b) (4)
- Updated clinical trial data to include WBC cystine efficacy data for patients ages 2 to 6 years old to support the changes in the treatment indication
- Included a general statement regarding WBC cystine levels during the extension trial for the patients who completed RP103-03; (b) (4) (see Sections 6.1.4 and 6.1.5).
- Included a general statement regarding the maintenance of mean estimated glomerular filtration rate (eGFR) in the RP103-03 patients with ongoing treatment in the extension trial; (b) (4)
- The Applicant’s proposal to include (b) (4) was not accepted (b) (4)

### Patient Counseling Information

- Reordered the subsections to present the information in order of clinical importance.
- Deleted (b) (4)

In addition to review team and DPMH consultants, the labeling was also reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP). Their comments and recommendations have been incorporated into final labeling. For final labeling agreements, the reader is referred to the approved label for Procysbi.

### **9.3 Advisory Committee Meeting**

No advisory committee meeting was held during the review of these supplemental applications.

## 9.4 Supplemental Information

### 9.4.1 RP103-04 Study Protocol Amendments

#### Amendment 1 (March 11, 2010)

- Eligibility Criteria:
  - Removed minimum weight eligibility criterion
  - Allowed enrollment of additional patients who are on a stable Cystagon dose after all patients from Study RP103-03 have been enrolled.
  - Required new subjects to be on a stable dose of Cystagon, considered by the Investigator as a suitable dose of cysteamine that produces a meaningful reduction in white blood cell (WBC) cystine levels, at least 21 days prior to Screening
- Study visits: (Modified clinic visit schedule)  
(This schedule was followed by all patients continuing from RP103-03)
  - Screening Visit:
    - For patients continuing from RP103-03, occurs simultaneously with RP103-03 Period 3, Day 3 Study visit
    - For patient entering the Study on a stable dose of Cystagon: Can occur up to 28 days prior to Day 1.
  - Monthly Visits beginning 1 month ( $\pm 7$  days) from last Study visit; planned completion of 6 consecutive Monthly treatment visits
  - Quarterly treatment visits beginning  $\geq 1$  month and  $< 4$  months after the patient has completed 6 consecutive Monthly treatment visits; Quarterly visits will take place during by the middle of the first month ( $\pm 7$  days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15), with up to 6 Quarterly treatment visits over this 2 year study, depending on enrollment
  - End of Study (EOS) Visit will be conducted within 7 ( $\pm 2$  days) from the last completed Study visit or from the date of termination.
- Procysbi Dosing and Administration:
  - Provided RP103 starting daily dose (70% of daily Cystagon dose) and maximum allowed dose (100% of daily Cystagon dose) for additional patients enrolled into trial (i.e., patients not entering from RP103-03)
  - Clarified patient administration instructions to:
    - Eat food immediately prior to administration of RP103 and withhold dairy products for 1 hour before and after RP103 administration
    - Take RP103 with an acidic beverage
- Study Assessments:
  - Eliminated exploratory endpoints of “gastrointestinal symptoms”

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- Changed self-report instrument to PedsQL, instead of parent proxy report
- Added safety and PK/PD data reviews during or prior to each study visit

(may be used for dose adjustments)

- Trough plasma cysteamine concentration to be measured from samples collected 1 hour post dose at each Study visit
- WBC cystine to be measured 1 hour post dose at each Study visit

### Amendment 2 (May 20, 2010)

- Eligibility Criteria:
  - Required patients to be on a stable Cystagon dose at trial entry (removed language (b) (4))
  - Changed inclusion criterion to (b) (4) “subject on a stable dose of Cystagon at least 21 days prior to Screening”
  - Eliminated requirement that “subject must be on a stable dose of Cystagon, considered by the Investigator as a suitable dose of cysteamine that produces a meaningful reduction in white blood cell (WBC) cystine levels” from inclusion criteria.
  - Defined “meaningful reduction in WBC cystine level” as  $<1 \text{ nmol } \frac{1}{2} \text{ cystine/mg protein}$  (although removed from inclusion criteria)  
*Refers to the statement In Section 4.4 (Dose Rationale), which states that “if a subject does not achieve a meaningful reduction of WBC cystine level or does not tolerate the dose, as determinate by the Investigator, the subject may have their RP103 dose adjusted or may be terminated from the Study.”*
  - Clarified liver and renal function eligibility criteria by providing specific cut-off values for liver enzymes and GFR
- Study Visits: Allowed patients receiving Cystagon at the conclusion of study RP103-02 to roll over into RP103-03 without a Day 1 study visit
- Assessments:
  - Changed to use of an investigator-administered VAS swallowing difficulty instrument instead of a patient-reported instrument
  - Changed PK and PD sampling time from 1 hour to 0.5 hours post RP103 dose administration *(to synchronize with changes incorporated in the precursor pivotal study RP103-03)*

### Amendment 3 (August 9, 2010)

[34/40 RP103-03 patients enrolled under Amendment 3]

- General: Required that RP103-03 trial be completed and data analyzed prior to opening

enrollment to additional patients

- Safety procedures:
  - Added stopping criteria that were consistent with RP103-03 Amendment 4
  - To correct the list of safety endpoints.

**Amendment 4 (May 2, 2011)**

*[6/40 RP103-03 patients enrolled under Amendment 4]*

- Procysbi Dosing and Administration:
  - Changed starting Procysbi dose to 80% of daily Cystagon dose (from 70%) and maximum allowed dose increased to 100% of daily Cystagon dose)—modified to align with dosing modifications made in RP103-03
  - Modified patient instructions to:
    - Fast for at least 3 hours prior to Procysbi dosing
    - Eat snack/meal 30-60 minutes after Procysbi dosing
- Enrollment Procedures: Clarified timing of enrollment and screening schedule for patients not entering from RP103-03
- Study Assessments: Described a correction factor for total protein used to allow comparison of WBC cystine levels measured by different methods

*(Since implementation, this correction factor has been applied to all WBC measurements, both prospectively and retrospectively, and datasets have been changed to reflect these calculations)*

**Amendment 5 (September 27, 2011)**

*[All 20 new patients enrolled under Amendment 5]*

- Eligibility Criteria: Expanded to permit enrollment of subjects who do not receive their cysteamine dose as intact capsules, and those who receive it via gastric tube.
- Study Visits:
  - Added 5-day Dose Confirmation Period for patients not entering from RP103-03
  - Eliminated Monthly Study Visits for patients newly enrolled in RP103-04 (only Quarterly Visit scheduled after completion of the Dose Confirmation Period)
- Procysbi Dosing and Administration:
  - Changed starting daily Procysbi dose to 70% of stable baseline Cystagon dose and allowed dose increases up to 100% of Cystagon dose
  - Allowed administration of opened capsules
  - Allowed administration of study drug (opened capsules) via gastric tube, and provided instructions for this method of administration

**Amendment 6:** (dated September 26, 2012, after all patients enrolled)

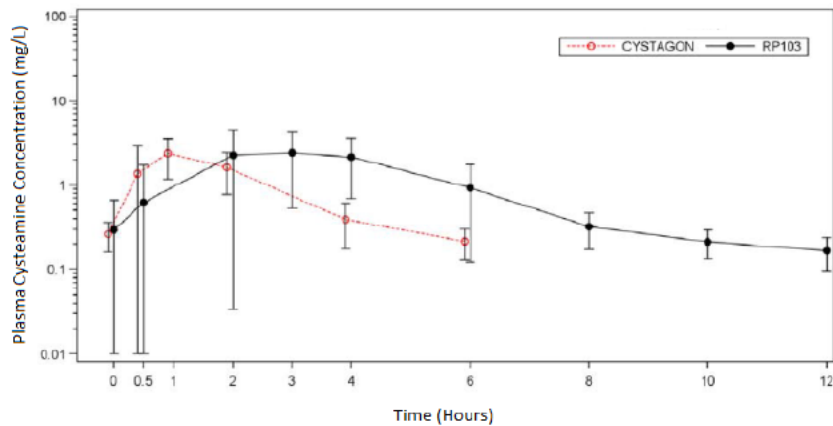
- Eligibility Criteria: Added exclusion criterion for patients <1 year old



- Study Duration: Increased maximum study duration from 24 to 36 months;
- Procysbi Dosing: Clarified statements and instructions pertaining to RP103 dosing;
- Study Assessments: Added an optional PK substudy visit for all subjects 6 years old and younger

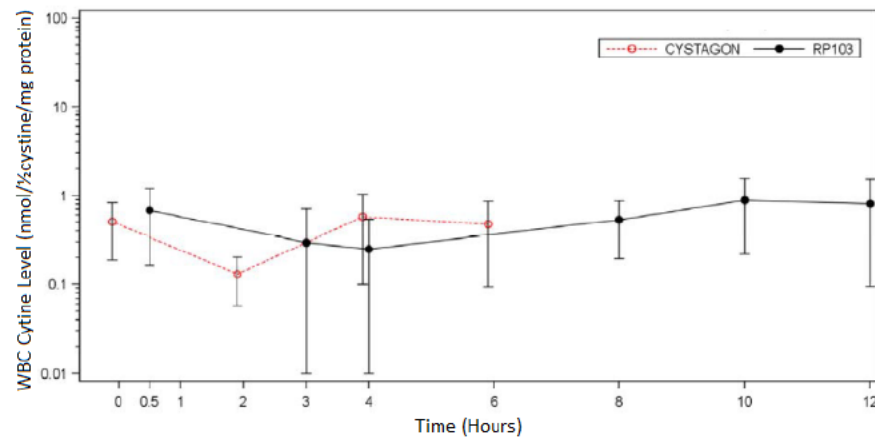
### 9.4.2 Additional Clinical Pharmacology Information

**Figure 33: Mean ( $\pm$ SD) Plasma Cysteamine Concentration vs. Time in RP103-03 Patients (N=39)**



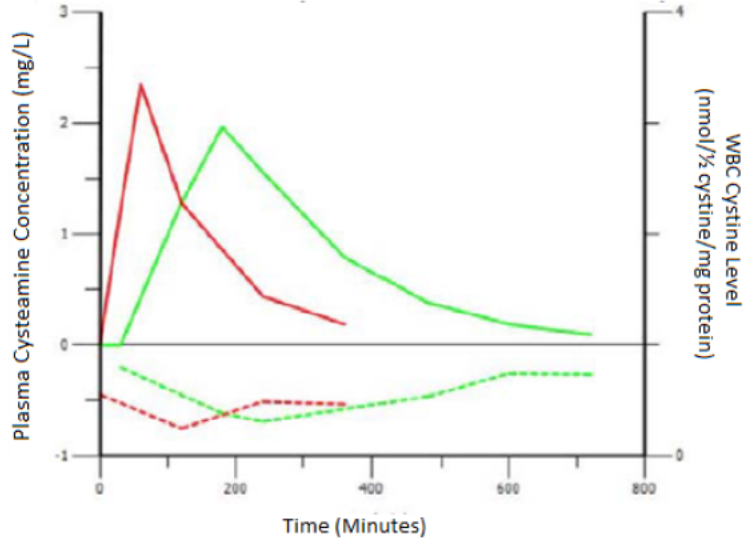
(Source: Clinical Pharmacology Review for original NDA review by Dr. Kristina Estes dated March 30, 2012)

**Figure 34: Mean ( $\pm$ SD) WBC Cystine Levels vs. Time in RP103-03 Patients (N=39)**



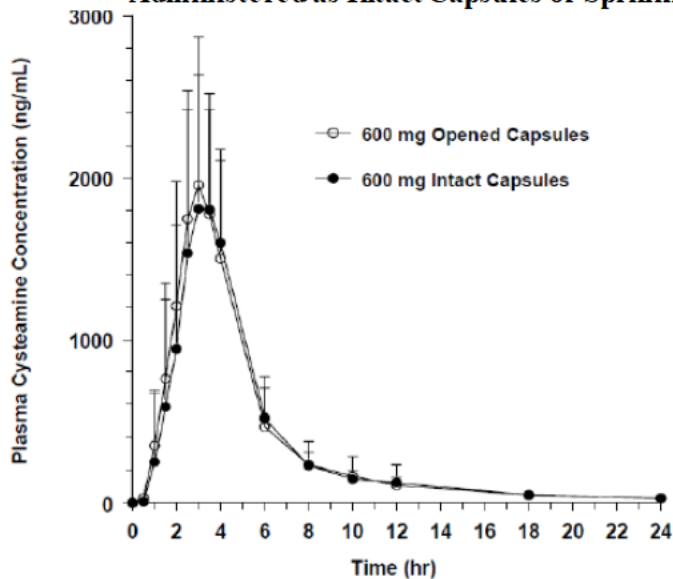
(Source: Clinical Pharmacology Review for original NDA review by Dr. Kristina Estes dated March 30, 2012)

**Figure 35: Procysbi Pharmacokinetics vs. Pharmacodynamics in RP 103-03 Patients**



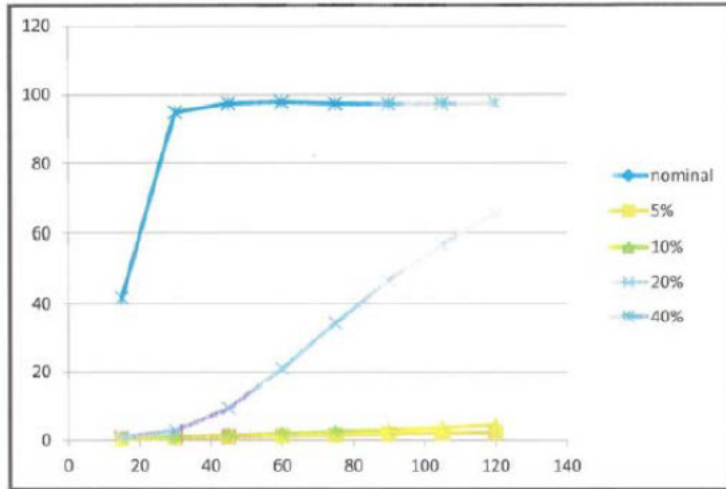
(Source: Clinical Pharmacology Review for original NDA review by Dr. Kristina Estes dated March 30, 2012)

**Figure 36: Mean Plasma Cysteamine Concentration Following a Single Dose of 600mg RP103 Administered as Intact Capsules or Sprinkled on Applesauce**



(Source: Clinical Pharmacology Review for original NDA review by Dr. Kristina Estes dated March 30, 2012)

**Figure 37: Alcohol Dumping of Procysbi**



(Source: Clinical Pharmacology Review for original NDA review by Dr. Kristina Estes dated March 30, 2012)

### **Food/liquid compatibility studies**

Stability studies were performed with (degassed), Fanta® (degassed, orange), Gatorade® (degassed, orange), PolyCitra, tap water (b) (4) apple sauce, peanut butter (smooth), strawberry yogurt (held at room temperature and 5°C), orange sherbet (held at room temperature until started to melt, ~ 20 minutes), and berry jelly. (b) (4)

(b) (4)  
The sponsor also performed a study to determine the ability to administer capsule contents through a feeding tube. Beads were administered in tap water and in applesauce. (b) (4)

(From CMC review by Dr. Jane Chang dated March 5, 2013)

### 9.4.3 Additional Efficacy Tables/Figures

**Table 30: Summary of WBC Cystine Concentrations Over Time (RP103-03 Subjects; PK/PD Population)**

Study Visit (0.5 Hrs. Post Dose)	Baseline (nmol $\frac{1}{2}$ cystine/mg protein)			Overall
	$\leq 1$	$\geq 1$ and $\leq 2$	$> 2$	
<b>Month 1</b>				
N	33	4	2	39
Mean (SD)	0.37 (0.327)	0.38 (0.187)	1.57 (1.933)	0.43 (0.513)
Median	0.23	0.39	1.57	0.31
Min, Max	0.05, 1.66	0.15, 0.61	0.21, 2.94	0.05, 2.94
<b>Month 2</b>				
N	33	4	2	39
Mean (SD)	0.40 (0.312)	0.71 (0.125)	0.70 (0.528)	0.45 (0.321)
Median	0.43	0.75	0.70	0.44
Min, Max	0.04, 1.36	0.53, 0.81	0.32, 1.07	0.04, 1.36
<b>Month 3</b>				
N	29	4	2	35
Mean (SD)	0.36 (0.323)	0.57 (0.220)	1.20 (1.113)	0.44 (0.410)
Median	0.20	0.63	1.20	0.33
Min, Max	0.03, 1.07	0.26, 0.77	0.42, 1.99	0.03, 1.99
<b>Month 4</b>				
N	31	4	2	37
Mean (SD)	0.36 (0.364)	0.59 (0.187)	0.79 (0.791)	0.41 (0.380)
Median	0.26	0.56	0.79	0.30
Min, Max	0.05, 1.87	0.40, 0.83	0.23, 1.35	0.05, 1.87
<b>Month 5</b>				
N	30	4	2	36
Mean (SD)	0.48 (0.426)	0.97 (0.241)	0.95 (0.499)	0.56 (0.442)
Median	0.44	0.99	0.95	0.58
Min, Max	0.05, 1.78	0.67, 1.24	0.59, 1.30	0.05, 1.78
<b>Month 6</b>				
N	32	4	2	38
Mean (SD)	0.38 (0.372)	0.83 (0.311)	1.02 (0.953)	0.46 (0.431)
Median	0.31	0.87	1.02	0.32
Min, Max	0.00, 1.54	0.46, 1.10	0.34, 1.69	0.00, 1.69
<b>Quarter 1</b>				
N	31	4	2	37
Mean (SD)	0.39 (0.277)	0.95 (0.456)	0.72 (0.601)	0.47 (0.355)
Median	0.44	0.84	0.72	0.50
Min, Max	0.04, 0.93	0.59, 1.55	0.29, 1.14	0.04, 1.55
<b>Quarter 2</b>				
N	32	4	2	38
Mean (SD)	0.33 (0.267)	1.07 (0.365)	0.51 (0.040)	0.42 (0.352)
Median	0.27	1.16	0.51	0.34
Min, Max	0.04, 1.28	0.56, 1.42	0.48, 0.54	0.04, 1.42

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**Table 30 (Continued)**

Study Visit (0.5 Hrs. Post Dose)	Baseline (nmol ½ cystine/mg protein)			Overall
	≤1	≥1 and ≤2	>2	
<b>Quarter 3</b>				
N	31	4	2	37
Mean (SD)	0.47 (0.371)	0.57 (0.390)	0.62 (0.303)	0.49 (0.363)
Median	0.39	0.51	0.62	0.42
Min, Max	0.04, 1.39	0.17, 1.10	0.40, 0.83	0.04, 1.39
<b>Quarter 4</b>				
N	31	4	2	37
Mean (SD)	0.49 (0.371)	0.52 (0.189)	0.45 (0.123)	0.49 (0.344)
Median	0.50	0.55	0.45	0.52
Min, Max	0.03, 1.40	0.27, 0.72	0.36, 0.54	0.03, 1.40
<b>Quarter 5</b>				
N	29	4	2	35
Mean (SD)	0.38 (0.351)	0.62 (0.308)	0.72 (0.040)	0.43 (0.349)
Median	0.29	0.55	0.72	0.32
Min, Max	0.04, 1.57	0.34, 1.06	0.69, 0.75	0.04, 1.57
<b>Quarter 6</b>				
N	25	4	1	30
Mean (SD)	0.57 (0.299)	0.53 (0.230)	0.25 (-)	0.56 (0.289)
Median	0.53	0.62	0.25	0.53
Min, Max	0.06, 1.37	0.19, 0.69	0.25, 0.25	0.06, 1.37

(Source: Applicant's Table 13, "Summary of WBC Cystine Concentrations Over Time (RP103-03 Subjects; PK/PD Population)", Interim Clinical Study Report, pages 75-76/201; NDA 203389, Module 5.3.5.2)

#### 9.4.4 Financial Disclosure Review

##### Clinical Investigator Financial Disclosure

Application Number: NDA 203389/ (b)(4) S-10  
 Submission Date(s): July 14, 2014  
 Applicant: Raptor Pharmaceuticals  
 Product: Procysbi

Reviewer: Lauren Weintraub, MD  
 Date of Review: August 13, 2015  
 Covered Clinical Study (Name and/or Number): RP103-04

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>32 (10 Investigators and 22 Sub-Investigators)</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		

Clinical Review  
 Lauren Weintraub, MD  
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 Procysbi (delayed-release cysteamine bitartrate capsules)

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

***Not applicable—there were no investigators with disclosable financial interests/arrangements.***

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LAUREN A WEINTRAUB  
08/13/2015

JESSICA J LEE  
08/13/2015