Office of Clinical Pharmacology Review

NDA or BLA Number	NDA203389/S20
Link to EDR	\\CDSESUB1\evsprod\NDA203389\0108
Submission Date	June 29, 2017
Submission Type	Priority
Brand Name	Procysbi®
Generic Name	Cysteamine bitartrate
Dosage Form and Strength	Delayed-release capsule
Route of Administration	Oral
Indication	Nephropathic cystinosis
Proposed Dosing	Starting dosage of Procysbi® for cysteamine-naïve patients is 0.2 to 0.3 grams/m^2 per day divided into two doses given every 12 hours. Maintenance dosage of Procysbi® for cysteamine-naïve patients is 1.3 gram/m^2 per day, divided into two equal doses given every 12 hours.
Applicant	Horizon Pharma
OCP Review Team	Jee Eun Lee, Ph.D., Jie Cheng Ph.D., Insook Kim, Ph.D., Justin Earp, Ph.D.
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1 EXECUTIVE SUMMARY

Procysbi® (cysteamine bitartrate) delayed-release capsules were approved on April 30, 2013 for the management of nephropathic cystinosis in adults and children 6 years and older. Its extension to use in children aged 2-5 years with nephropathic cystinosis was approved on August 14, 2015. Upon approval, the agency issued a formal Written Request dated August 19, 2013 and amended on October 6, 2015 asking the applicant to evaluate the safety and effectiveness of Procysbi in cysteamine-naïve pediatrics patients aged birth to < 6 years. The applicant proposes to extend the indication to patients < 2 years old with the current application. In this submission, the applicant also requests the determination of pediatric exclusivity based on Study RP103-08 (NCT01744782), an open-label PK/PD, safety and efficacy study in pediatric patients with nephropathic cystinosis aged birth to < 6 years.

The clinical efficacy of Procysbi® in cysteamine treatment-naïve patients with cystinosis is supported by the data obtained from Study RP103-08 where 17 subjects were enrolled (15 subjects <6 years, 2 subjects older than 6 years) and 16 of them completed the study (1 patient <6 years died during the study). Pharmacokinetics (PK) and pharmacodynamics (PD) data in treatment-native patients <6 years in Study RP103-08 were compared with those in patients 6 years and older from previously completed studies (Study RP103-03 and its extension Study RP103-04) by the applicant and additionally by the reviewer, which led to a conclusion that PK-PD relationship for WBC cystine in cysteamine-naïve pediatric patients with 2-5 years of age are comparable with pediatric patients 6 years and older and adults. Furthermore, the submitted data included PK-PD in 1-year old children (N=7), for whom Procysbi® was not indicated. The PK-PD in 1-year old children appears to be comparable with that in children ≥2 year of age and is supportive of use of Procysbi® in 1-year old patients. No patients younger than 1 year of age were enrolled in Study RP103-08.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the submitted data and found acceptable to support administration of Procysbi® in treatment-naïve pediatric patients with 1 to 5 years of age. Study RP103-08 was conducted in compliant with the Written Request from a clinical pharmacology perspective.

1.2 Post-Marketing Requirements and Commitments

Not applicable.

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics and Pharmacodynamics

Nephropathic cystinosis is an autosomal recessive disease caused by mutations in the CTNS gene that encodes the lysosomal cystine transport protein resulting in accumulation of the amino acid cysteine within the cells. Untreated patients with nephropathic cystinosis may experience end-stage renal failure usually before 10 years of age and may require renal transplantation. Cysteamine bitartrate reacts with intra-lysosomal cysteine to form the mixed disulfide of cysteamine and cysteine and then cysteine be released from the lysosome via the lysine transport system.

Study RP103-08 (Study 08) was an open label study to assess safety and effectiveness of long-term repeat dosing of Procysbi® on white blood cell (WBC) cystine concentration in nephropathic cystinosis patients <6 years of age who were naïve to cysteamine treatment. The study also evaluated a new treatment initiation and titration methodology designed to maximize tolerability of Procysbi® in treatment-naïve patients.

The pharmacokinetics of Procysbi® at steady state were evaluated in 11 cysteamine treatment-naïve patients 1 5 years of age with nephropathic cystinosis. A mean (± SD) C_{max} of 1.26 ± 0.86 mg/L was reached at an average T_{max} of 199 ± 138 minutes. The mean exposure was estimated to be 206 ± 113 min*mg/L (AUC_{last}) and 231 ± 123 min*mg/L (AUC_{inf}). The mean CL_{ss}/F was estimated to be 0.69 ± 0.37 L/min with an average half-life ($t_{1/2}$) of 270 ± 56 minutes. The estimated C_{max} and AUC at steady state (at 6 months after treatment initiation) from treatment-naïve pediatric patients 1-5 years of age in Study RP103-08 were lower than those in patients ≥ 6 years of age observed at the end of Study RP103-03 who were continuously enrolled into Study RP103-04. The lower cysteamine concentrations were due to lower maintenance doses in Study RP103-08. Nevertheless, the pharmacokinetic and pharmacodynamic profiles over time up to Month 18 in cysteamine-naïve pediatric patients 1-5 years of age observed from Study RP103-08 were within the range of those in children ≥ 6 years of age observed from Study RP103-04. Overall, PK-PD in patients between the ages of 1 and 5 years of age is comparable with that in older children and adults.

2.1.1 General dosing

The proposed initial and maintenance doses for the treatment-naïve patients 1-5 years of age are the same as the currently approved initial and maintenance dose for patients ≥2 years of age (Table 1). In addition, dose is to be adjusted based on the WBC cystine concentrations and tolerability.

Table 1. Recommended Targeted Procysbi ® Maintenance Dose for Subjects <6 Years

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

(Source: RP103-08, Clinical Study Report, Table 9-2)

The applicant does not propose to change the approved doses for the treatment-naïve pediatric patients ≥2 years of age.

- Start treatment with a dosage equal to 1/6 to ¼ of the maintenance dosage.
- The maintenance dosage after initial dose escalation is 1.3 g/m^2 of body surface area per day divided into two doses given every 12 hours.

One of the objectives of the Study RP103-08 was to evaluate the approved dose in treatment-native patients. Although Procysbi was approved in cysteamine treatment-naïve patients, the original approval was based on the control of WBC cystine in patients who were switched from the immediate-release cysteamine product; therefore, Procysbi® was not studied in treatment-naïve patients. Accordingly, patients enrolled in Study RP103-08 were treated with the approved initial dose and titration scheme, i.e., 10% increment, however the target maintenance dose, i.e., 1 gram/m^2/day was lower than the approved 1.3 gram/m^2/day. The WBC cystine levels in subjects <6 years in Study RP103-08 tended to be in higher than that in Study RP103-03 (Study 03) where the maintenance dose ranged 1-3 g/m^2/day. Consequently, cysteamine concentrations tended to be lower in Study RP103-08 than those in Study RP103-03 especially when lower than recommended maintenance doses were administered. Moreover, the proposed initial and maintenance doses for 1 year old patients, which are the same as doses for patients ≥ 2 years, are acceptable.

In Study RP103-08, Procysbi® was administered orally as an intact capsule or its content sprinkled onto soft foods such as apple sauce. Some patients, especially younger patients received Procysbi® via gastrostomy tube (G-tube). Administration of Procysbi® via G-tube or after mixing with soft foods is recommended in the approved label.

2.2 Summary of Labeling Recommendations

The proposed labeling update for the PK of cysteamine in treatment-naïve patients in Section 12.3 is acceptable. However, the labeling should state the PK of cysteamine in pediatric patients younger than 1 year old. Detailed labeling recommendation will be conveyed separately.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Procysbi® (cysteamine bitartrate) delayed-release capsules were approved on April 30, 2013 for the management of nephropathic cystinosis in adults and children 6 years and older based on the safety and effectiveness of Procysbi® evaluated in Study RP103-03 in subjects who previously received Cystagon®, immediate-release formulation of cysteamine bitartrate. Its extension to use in children aged 2-5 years with nephropathic cystinosis was approved on August 14, 2015, based on data obtained from newly enrolled patients in Study RP103-04, an extension study of RP103-03. Procysbi® is comprised of enteric coated beads of cysteamine bitartrate encapsulated in gelatin capsules to be administered every 12 hours.

To obtain needed pediatric information on cysteamine bitartrate, the Agency issued a formal Written Request dated August 19, 2013 and amended on October 6, 2015. As a response to the Written Request, the applicant submitted the current application with completion of Study RP103-08 titled, "An Open-Label, Safety and Effectiveness Study of Cysteamine Bitartrate, Delayed-release Capsules (RP103) in Cysteamine Treatment Naïve Patients with Cystinosis." A total of 17 subjects including 15 subjects < 6 years of were enrolled in Study RP103-08. The clinical efficacy of Procysbi® in cysteamine treatment-naïve patients with cystinosis is supported by data obtained from Study RP103-08.

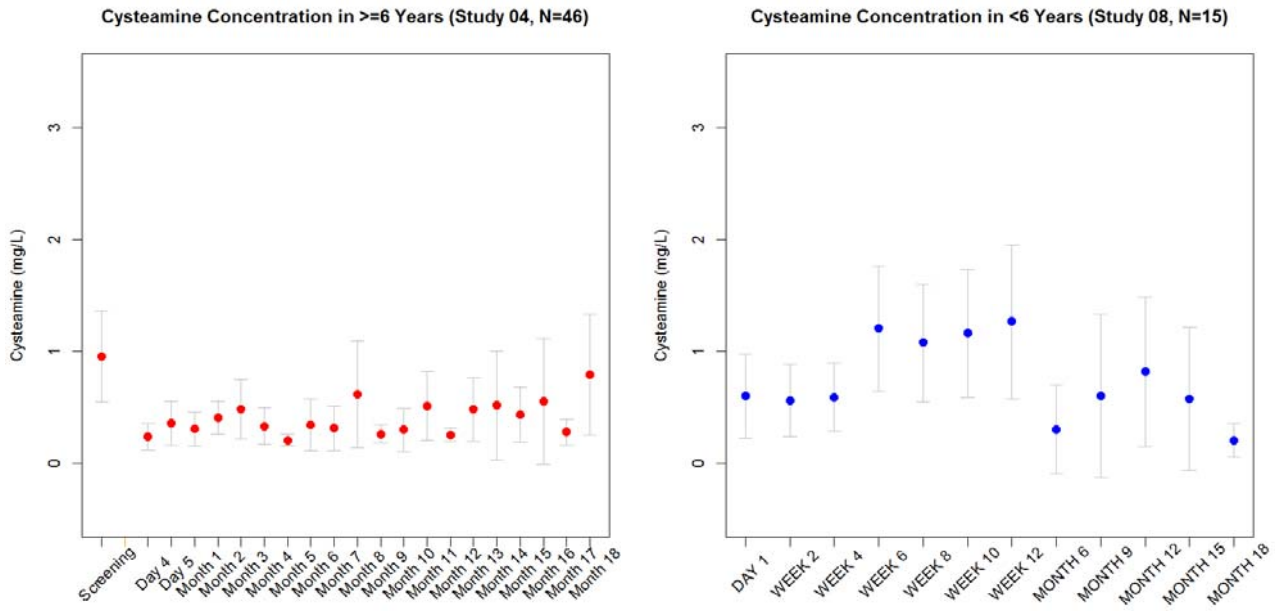
3.2 Clinical PK-PD and Safety-PD Assessments

3.2.1 Does the available clinical pharmacology information provide supportive evidence of effectiveness and safety in cysteamine-naïve patients 1- 6 years of age with nephropathic cystinosis?

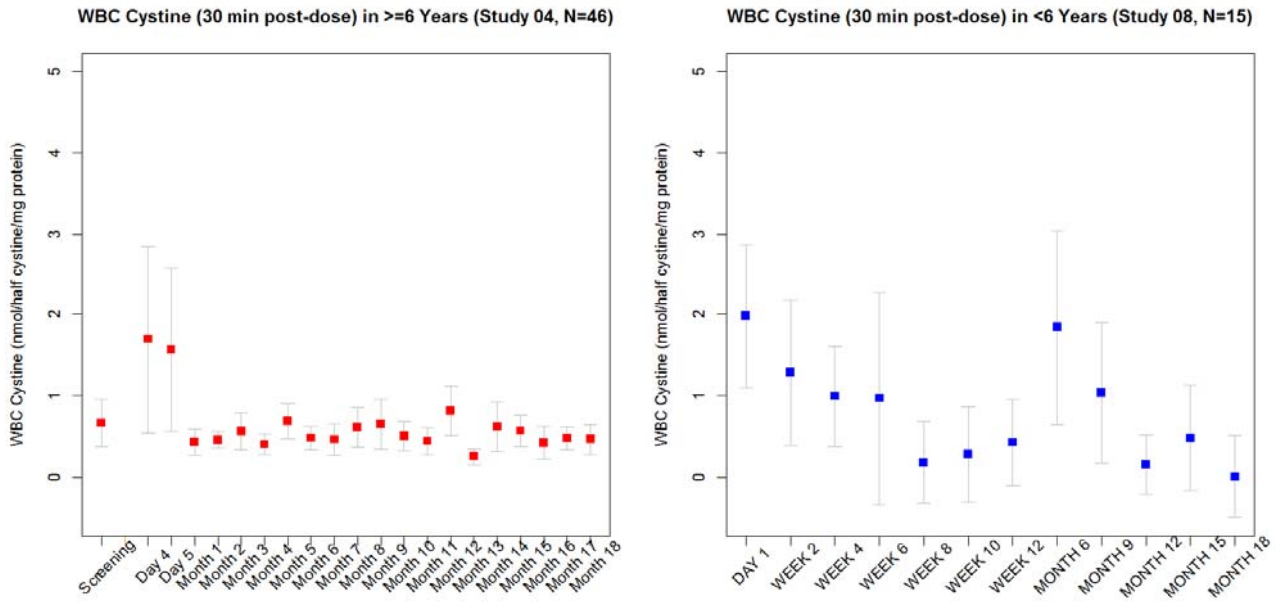
Yes. The applicant performed a non-compartmental analysis with data obtained from the Month 6 visit in Study RP103-08 and then compared with those obtained from older children and adults in Study RP103-03 (at Screening for RP103-04 which can be considered at steady state referenced to Study RP103-03). As shown in Figure 1, the PK-PD profiles over time up to Month 18 in treatment-naïve pediatric patients 1-5 years of age observed from Study RP103-08 were within the range of those in children 6 years of age or older observed from Study RP103-04. Among the subjects enrolled in Study RP103-04, subjects who were previously treated with either Cystagon® or Procysbi® in Study RP103-03 (N=40) and newly enrolled subjects after renal transplantation (N=6)

were briefly treated with Cystagon® during the Screening, were included in the analysis.

Figure 1. Comparison of Cysteamine Concentration and WBC Cystine Concentration-Time Profiles between Children <6 Years (Study RP103-08) and Older Children and Adults (RP103-04)



(a) Cysteamine Concentration Profile over Time

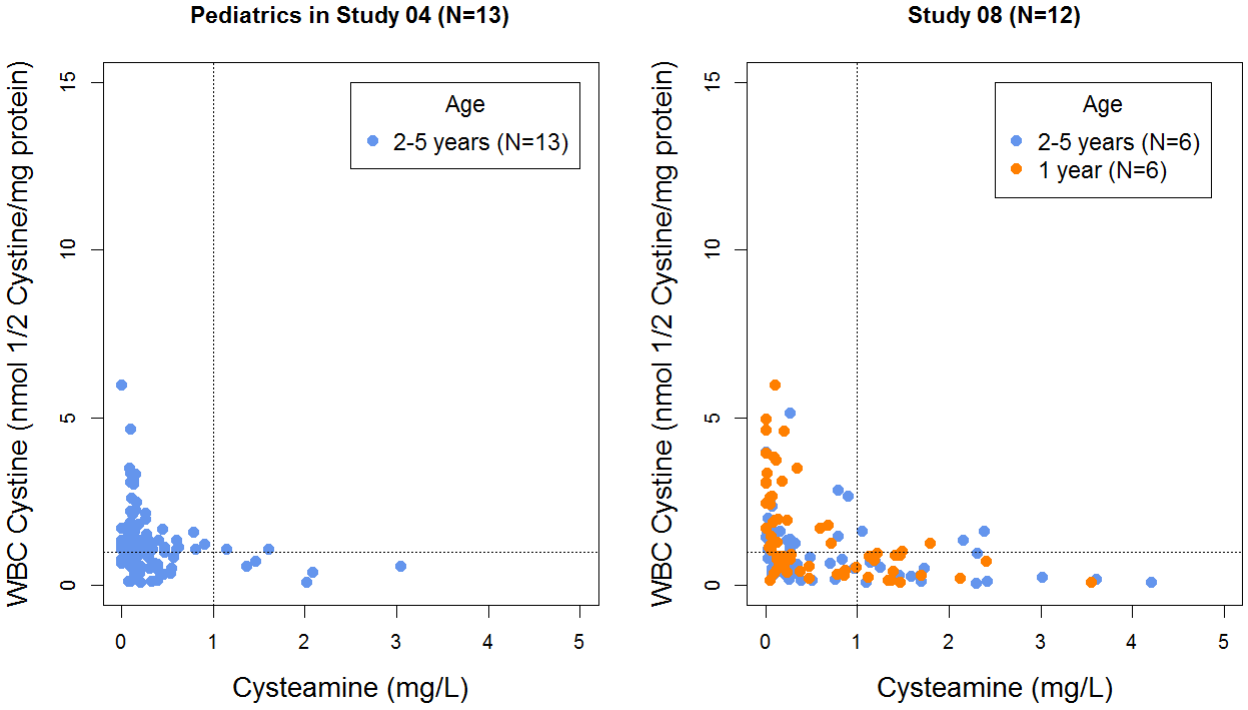


(b) WBC Cystine Profile over Time

(Source: Reviewer's analysis, data from Study 04 was truncated up to Month 18)

The PK-PD relationship in treatment-naïve patients 2-5 years of age from Study RP103-08 was also comparable with that in patients 2-5 years of age who received Cystagon® during the Screening and then switched to Procysbi® in Study RP103-04 (Figure 2). As shown in Figure 2, the exposure-response (ER) relationships for WBC cystine level between patients 2-5 years old in RP103-08 and those in RP103-04 are similar for those of who had similar baseline WBC cystine levels. There were 3 subjects whose baseline WBC cystine level was much higher (WBC cystine above 4 nmol ½ cystine/mg protein) than that in other subjects in Study RP103-08 or Study RP103-04, so the comparison for the absolute values of WBC cystine was made without those 3 subjects in Figure 2. Further analysis for an alternative PD endpoint, the percent (%) change from baseline, confirmed that those subjects with higher baseline cystine also showed similar exposure-response relationships with those in other subjects when % change from baseline was compared (see Section 3.4.4.2).

Figure 2. Exposure-Response Relationships between 30-Minute Post-Dose Cysteamine and WBC Cystine Concentrations in Children <6 Years in Study RP103-04 and in Study RP103-08



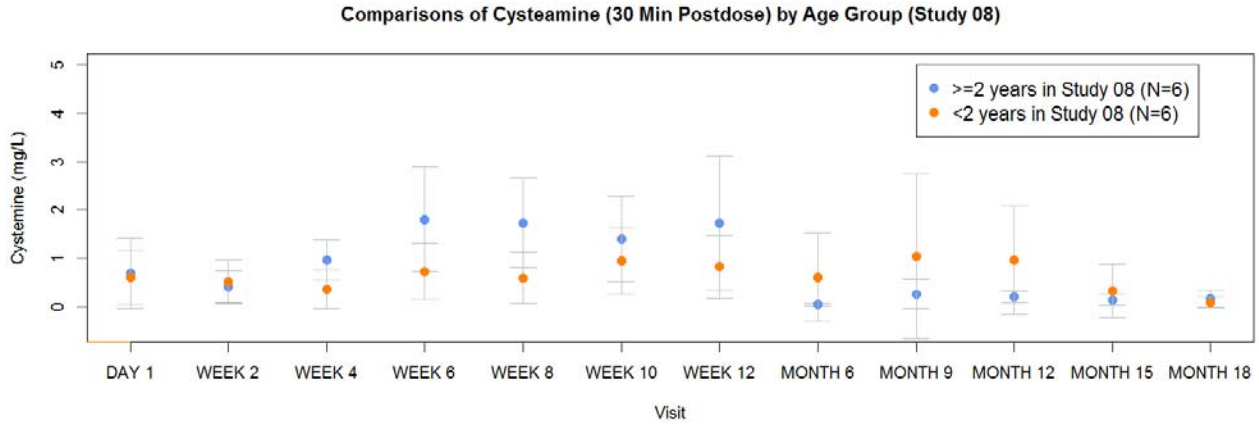
(Source: Reviewer's analysis, subjects whose baseline WBC cystine concentrations above 4 nmol ½ cystine/mg protein were not included. Analyses including those subjects are shown in Section 3.4.4.1 and Section 3.4.4.2)

The applicant also performed PK-PD analysis for safety endpoints per the PWR. Regarding to the PK-PD assessment for safety endpoints requested in the written request, the sponsor conducted analysis and submitted the results in response to the information request issued on September 7th, 2017, the PK-safety assessments indicated that cysteamine exposure (e.g., $AUC_{0\text{-}24h}$, C_{0h}, and C_{max}) over time has no correlation with safety endpoints including liver, renal, hematological parameters (AST, ALT, GGT and CBC (hemoglobin, hematocrit, platelet count, and WBC), GFR, blood pressure (hypertension) and proteinuria.

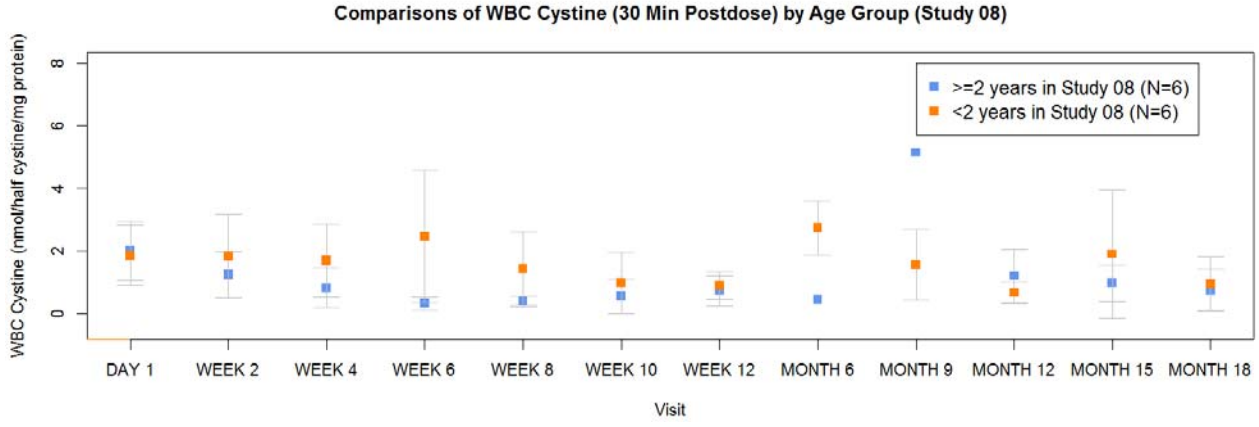
3.2.2 Is the PK-PD supportive to extend the indication to patients 1 year old?

Yes. To address this question, the reviewer compared longitudinal PK-PD between 1 year old patients and patients 2-5 years old since PK-PD comparison with intensive sampling was not available for patients <2 years of age. As shown in Figure 3, the PK-PD in patients 2-5 years and that 1 year old patients appear to be comparable and the similarity of PK-PD is supportive of extension of indication to patients 1 year old.

Figure 3. Comparisons of Cysteamine Concentrations and WBC Cystine Levels at 30-minute post-dose over Treatment duration between Children ≥2 Years and Children <2 Years in Study RP103-08



(a)



(b)

(Source: Reviewer's analysis, (a) PK; (b) PD)

3.2.3 Can the effect of administration method adequately be assessed?

No. Within the group of subjects age <6 years, comparisons of PK parameters by route of drug administration (oral [whole capsule], intragastric [via G-tube], and dietary [sprinkled onto food])

were planned by the applicant but were not conducted due to too small number of subjects in each group. Available data from Study RP103-08 indicate that among 15 subjects <6 years of age, 11 subjects received Procysbi® at least once orally or dietary, and 6 subjects received Procysbi® at least once via G-tube. One subject started with 50 mg of Procysbi® via G-tube, then received gradually increased doses (100, 150, and 250 mg per day) mixed with food, then switched back to G-tube for higher doses (250, 300, 450 mg per day). Two subjects started treatment with Procysbi® by mixing with allowed soft food and then switched to G-tube for higher daily dose. Only 3 subjects received Procysbi® via G-tube for the entire study duration. Therefore, any meaningful analysis could not be performed to evaluate the effect of administration method on PK-PD of Procysbi® with given data.

3.3 Applicant's Analysis

3.3.1 Noncompartmental PK Analysis

The objective of the analysis was to evaluate the PK and PD of Procysbi® in young patients including infants and children <6 years old with nephropathic cystinosis. Blood samples for determination of plasma cysteamine concentration were collected at the following times:

- Day 1
- Bi-Monthly Visits (30 minutes after the morning Procysbi® dose);
- Quarterly and Study Exit visits (30 minutes after the morning Procysbi® dose, 20-35minutes post dose for subjects enrolled under Protocol Amendment 1 or later)
- Quarterly Visit #1 (Month 6; 30 minutes after the morning PROCYSBI dose prior to Protocol Amendment 1; or 0 hour [pre-dose] and 30 minutes, 2, 3, 4, 6, 8, 10 and 12 hours after the morning Procysbi® dose Protocol Amendment 1 or later). Two of the Month 6 sampling times were time-matched with PD sample collection (WBC cystine) (Protocol Amendment 1 or later).

Plasma cysteamine concentrations were determined using a validated hydrophilic interaction liquid chromatography (HILC) high-pressure liquid chromatography (HPLC) tandem mass spectrometry (HPLCMS/MS) method.

The PK analyses for RP103-08 focused on the 14 subjects in the PK Population who were younger than 6 years of age (1 subject aged 3 who died after Visit 2 was excluded). Demographic and baseline characteristics for these 15 subjects are provided in Table 2.

Table 2. Demographic and Baseline Characteristics (Subjects <6 Years, N=15)

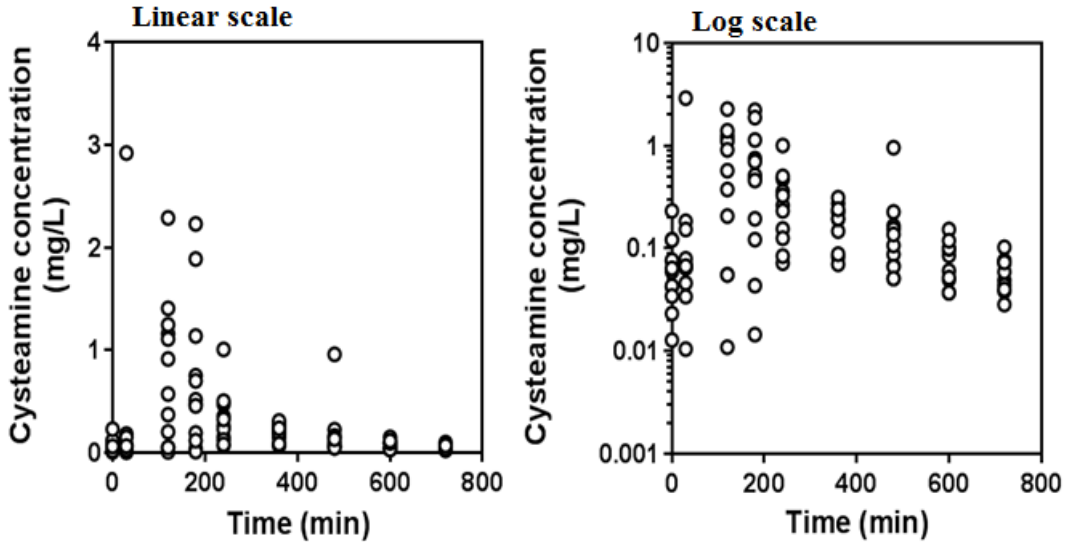
Characteristic		Mean [range]	N
Age (years)		2.22 [1.04, 4.53]	15
Gender	Male		8
	Female		7
Ethnicity	Hispanic or Latino		11
	Others		4
Weight (kg)		9.01 [5.80, 13.20]	15

(Source: Summary of Efficacy, Table 3, page 78)

All 15 subjects participated in the sparse PK and PD blood sampling on Day 1, Bi-Monthly, Quarterly, and Study Exit visits. Twelve of the subjects age <6 years participated in the frequent sampling at Month 6. Among these 12 subjects, one subject (01-013)'s intensive PK data were missing so the number of subjects included in the analysis for intensive sampling was 11.

A total of 32 PK-PD pairs from 12 subjects were utilized for PK-PD model development. The plasma cysteamine concentration-time profiles for the 11 subjects age <6 years at Month 6 are shown in Figure 4 on linear and log scales.

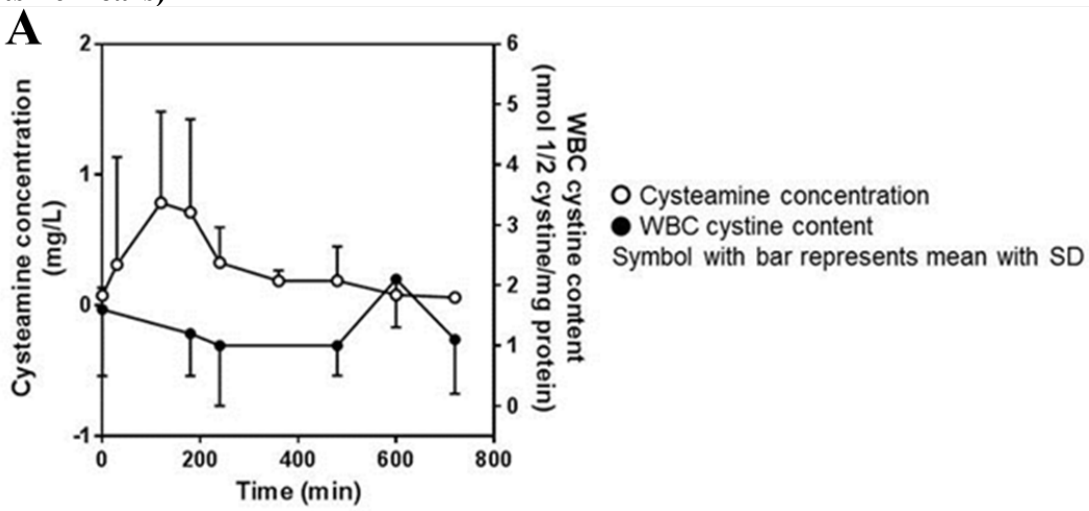
Figure 4. Cysteamine Concentration at Month 6 (Subjects <6 Years)



(Source: RP103-08 Clinical Study Report, Figure 11-2, page 101)

Pooled plasma cysteamine concentration-time profiles plotted with WBC cystine concentration at Month 6 are shown in Figure 5. The WBC cystine content decreased when the plasma cysteamine concentration increased, as expected based on the mechanism of drug action.

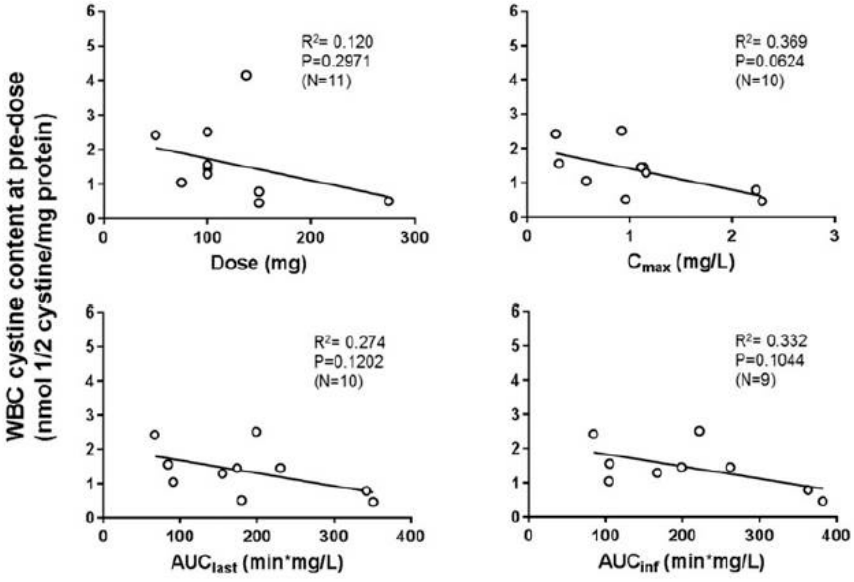
Figure 5. Mean (±SD) Cysteamine Concentration and WBC Cystine Level versus Time (Subjects <6 Years)



(Source: RP103-08 Clinical Study Report, Figure 11-3, page 102)

The relationship between individual PD data (WBC cystine concentration) at time 0 (pre-dose) and obtained PK parameters at steady state was investigated for subjects age <6 years. From the evaluation of potential associations between the pre-dose PD response with dose and PK parameters, C_{max} showed higher correlation (R^2= 0.369) compared to dose and the other PK parameters but was not statistically significant. (Figure 6).

Figure 6. Relationship between PK Parameters and Pre-dose PD response at Month 6 (Subjects <6 Years)



(Source: RP103-08, PK-PD Analysis Report, Figure A-10, page 52)

The applicant also compared the results across the studies. Pharmacokinetic parameters estimated using non-compartmental analysis (NCA) were summarized in Table 3 for the subjects <6 years of age who participated in frequent PK blood sampling at Month 6.

Table 3. Comparison of PK Parameters for Cysteamine Between Subjects <6 Years of Age and Older Subjects

Parameters	Children < 6 years old (Study RP103-08; at Month 6 Visit) Mean ± SD	Older children and adults (> 6 years) * Mean ± SD
Dose (mg)	121.9 ± 56.4	769 ± 239
BSA (m^2)	0.48 ± 0.08	1.16 ± 0.28
Dose/BSA (mg/m^2)	253.9 ± 117.5	662.9 ± 206.0
Age (years)	2.8 ± 1.0	11.9 ± 4.38
Body weight (kg)	10.0 ± 2.4	35.07 ± 12.20
C_{max} (mg/L)	1.26 ± 0.86	3.59 ± 1.70
T_{max} (min)	199 ± 138	186 ± 86
AUC_{last} (mg·min/L)	206 ± 113	739 ± 334
AUC_{inf} (mg·min/L)	231 ± 123	785 ± 358
CL/F (L/min)	0.69 ± 0.37	1.17 ± 0.72
Vd/F (L)	241 ± 118	386 ± 271
$T_{1/2}$ (min)	270 ± 56	230 ± 80

(Source: RP103-08, PK-PD Analysis Report, Table 8, page 38)

Mean (± SD) C_{max} of 1.26 ±0.86 mg/L was reached at an average time to maximum concentration (T_{max}) of 199 ±138 minutes. The mean exposure was calculated to be 206 ±113 min*mg/L (AUC_{last}) and 231 ±123 min*mg/L (AUC_{inf}). The mean oral clearance at steady state (CL_{ss}/F) was estimated to be 0.69 ±0.37 L/min with an average half-life ($t_{1/2}$) of 270 ±56 minutes.

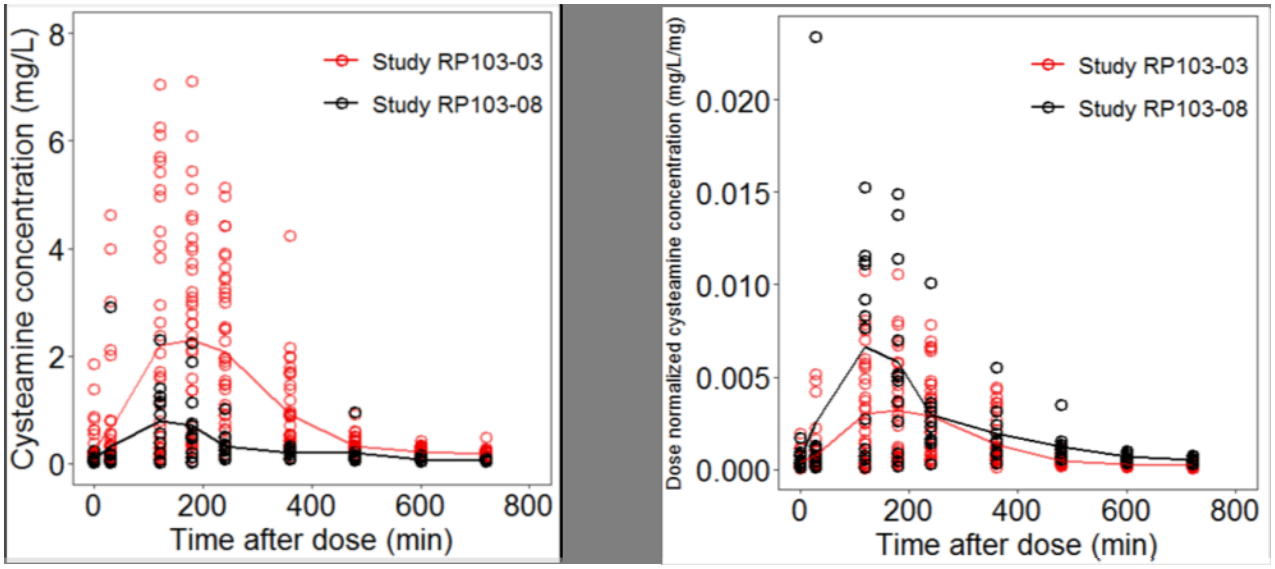
Reviewer's comments: Lower clearance in subjects <6 years of age (0.69 L/min) compared to that in subjects ≥6 years of age (1.17 L/min) appeared to be reasonable considering lower body weight. Mean body weight for subjects <6 years of age and those ≥6 years of age were 10 kg and 35.07 kg, respectively, and body weight was identified as a significant covariate for clearance from the population PK analysis. However, both C_{max} and AUC were lower in subjects <6 years of age compared to those in subjects ≥6 years of age, which appeared to be caused by lower than desirable doses in subjects <6 years of age. Per the approved label and the protocol for Study RP103-08, the recommended Procysbi® dose is 300 mg for a subject with 10 kg and 800 mg for a subject with

35.07 kg (see Table 1). However, subjects <6 years of age who participated in intensive sampling at Month 6 received 121.9 mg prior to the 12-hour intensive sampling, which indicates that these subjects were potentially under dosed. The PK-PD profiles over time show that cysteamine concentrations at Month 6 are lower than other visits (Figure 1), and WBC cystine levels are higher at Month 6 than other visits reflecting under-exposure. Since Procysbi® doses were adjusted based on WBC cystine level, the potential under dosing at Month 6 appear to be transient. Thus, the lower C_{max} and AUC of cysteamine caused by under dosing at Month 6 should not lead to a conclusion that cysteamine PK in subjects <6 years of age is not comparable to that in subjects ≥6 years of age.

Within the group of subjects<6 years, comparisons of PK parameters by age (infants versus children) and by drug administration method (oral [whole capsule], intragastric [via G-tube] and dietary [mixing with soft food]) were planned. The applicant concluded the analyses for the effect of age were not feasible because of the small sample size for infants (1 year of age, N=2), and it was also difficult to draw a definitive conclusion for the effect of administration method due to the small sample size.

Furthermore, the applicant compared PK-PD in pediatric patients <6 years of age and other pediatrics patients >=6 years of age and adults. The PK-PD profiles for subjects age <6 years were compared to those in older children and adults enrolled in Study RP103-03. To compare the plasma cysteamine PK profiles and the WBC cystine content over time in subjects <6 years to those in older children and adults, the data were overlaid with data from a previous study of Procysbi® (PK in Figure 7, PD in Figure 8).

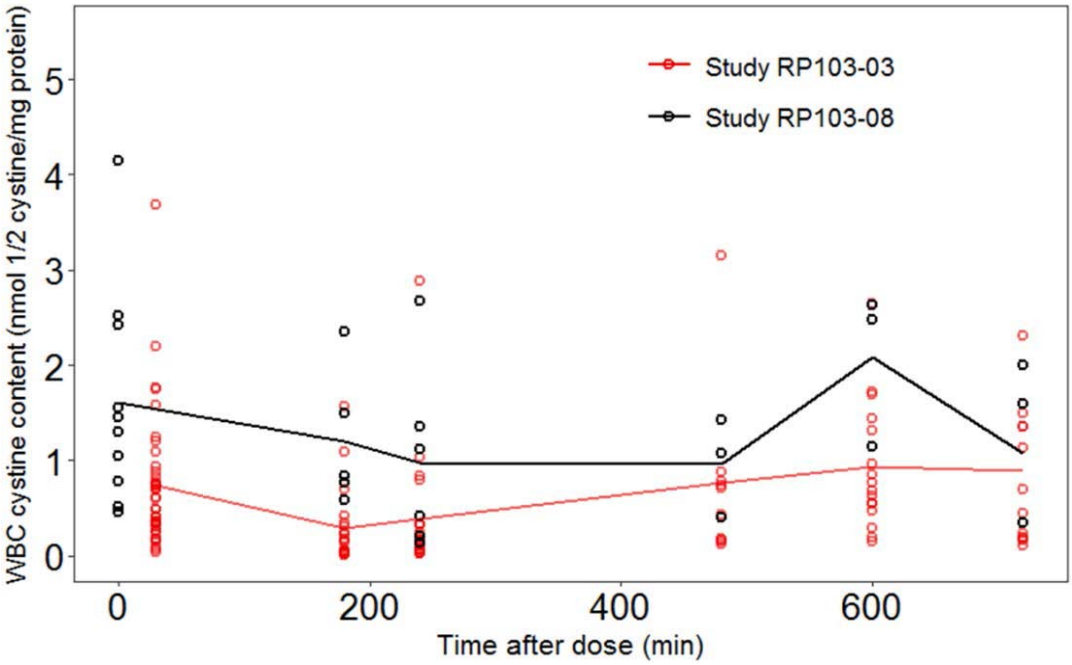
Figure 7. Comparison of Cysteamine Concentration-Time Profiles in Subjects <6 Years at Month 6 (Study RP103-08) versus Older Children and Adults (Study RP103-03)



(Source: RP103-08, PK-PD Analysis Report, Figure 3, page 26)

The WBC cystine levels in subjects age <6 years were at the higher end of that in Study RP103-03 and these PD levels were correlated with the lower cysteamine exposures in Study RP103-08. The applicant explained that the difference in cysteamine concentrations between these two group was caused by the difference in dosing. The recommended Procysbi® targeted maintenance dose in Study RP103-08 was 1 gram/m^2/day, in two divided doses given every 12 hours per protocol; whereas, in Study RP103-03, the dose ranged from 1 to 3 gram/ m^2/day. The data suggest children <6 years in Study RP103-08 were potentially under-dosed.

Figure 8. Comparison of WBC Cystine Concentration in Subjects <6 Years at Month 6 (Study RP103-08) versus Older Children and Adults (Study RP103-03)



(Source: RP103-08, PK-PD Analysis Report, Figure 4, page 27)

Reviewer's comments: The applicant's comparison of PK in pediatric patients <6 years of age and other pediatrics patients >=6 years of age and adults was done using dose-normalized cysteamine concentrations (right panel in Figure 7). The adequacy of dose and dose adjustment scheme for any specific population including pediatric patients should be evaluated with regards to absolute concentration. This can then be considered in relation to targeted response when similar exposure-response relationship is assumed between the reference population and the population of interest. Thus, the left panel in Figure 7 is the ideal comparison; however, the difference between the profiles of two populations is heavily influenced by the dose difference.

3.3.2 Population PK Analyses

The applicant performed a population PK analysis to compare estimated PK parameters between children <6 years and children >=6 years and adults. A total of 103 cysteamine concentrations collected from the intensive PK sampling were included in the analysis. A two-compartment model with first-order and lag time absorption adequately described the observed cysteamine concentration data. To account for body size difference, PK parameters of CL/F and apparent volume of distribution of central compartment (Vc/F) of Procysbi® were allometrically scaled to body weight (standardized to 70 kg) with fixed power of 0.75 for CL/F and 1 for Vc/F. However, the scaling was added to the typical clearance rather than individual clearance which led to inadequate assessment of individual clearance for subjects of interest. Goodness-of-fit showed the final model reasonably describes the PK data of Procysbi®.

Population PK parameter estimates for a typical subject with 70 kg obtained from the analysis with RP103-08 data were compared to those estimated from a separate analysis with data from Study RP103-03 (Table 4). The applicant reported the population estimates of cysteamine CL/F and Vc/F obtained from RP103-08 as those in subjects age <6 years but they should be interpreted as population estimates for a subject with 70 kg. Nonetheless, estimated cysteamine CL/F and Vc/F were 2.73 L/min and 393 L, respectively, which were higher than those estimated with data from older children and adults (CL/F: 2.15 L/min; Vc/F: 210 L).

Table 4. Comparison of Population PK Parameter Estimates in Subjects <6 Years (Study RP103-08) versus Older Children and Adults (Study RP103-03)

Parameter	Children Age <6 Years (Study RP103-08)	Older Children and Adults Age >6 Years (Study RP103-03)
Ka (1/min)	0.02	0.014
Lag time (min)	58.8	88.5
CL/F (L/min/70 kg)	2.73	2.15
Vc/F (L/70 kg)	393	210

(Source: RP103-08, PK-PD Analysis Report, Table 9, page 39)

Reviewer's comments: Performing the population PK and PK-PD analyses with pooled data including all measurements from Study RP103-03, RP103-04 and RP103-08 could have provided better estimates for PK-PD models, which could be also utilized to predict PK-PD in younger pediatric subjects, e.g., infants <1 year of age. Moreover, the applicant's final model estimated individual clearance inadequately. Allometric scaling for body weight should be added to individual clearance rather than population clearance for a typical subject with body weight of 70 kg. By doing so, the applicant obtained individual clearance estimates which are variable from a subject with 70 kg.

Plasma cysteamine levels were correlated with reductions in WBC cystine content, which were described by a direct inhibitory maximum effect (E_{max}) model through a population PK-PD modeling. As shown in Table 5, the starting (pre-dose) level of WBC cystine (E_0) at steady state (Month 6 Visit) was higher in subjects age <6 years than in older children and adults. The applicant discussed that this baseline value could be largely influenced by the Procysbi® dosage, this was not unexpected since the average dosage in Study RP103-08 was lower than in Study RP103-03. The concentrations producing 50% of the maximal inhibition (EC_{50}) were very similar between the two populations (0.78 mg/L versus 0.72 mg/L, Table 5).

Table 5. Comparison of Population PD Parameter Estimates in Subjects <6 Years (Study RP103-03) versus Older Children and Adults (Study RP103-03)

Parameter	Children Age <6 Years (Study RP103-08)	Older Children and Adults Age >6 Years (Study RP103-03)
Pre-dose E_0 (nmol ½ cystine/mg protein)	1.36	0.70
EC_{50} (mg/L)	0.78	0.72

(Source: RP103-08 PK-PD Analysis Report, Table 10, page 40)

Reviewer' comments: The baseline WBC cystine levels may influence individual patient's response to Procysbi® treatment in addition to the dosage. The difference in the estimated pre-dose E0 between these two populations truly reflected the difference in disease conditions between the patients enrolled in Study RP103-03 and Study RP103-08. There were 3 subjects enrolled in Study RP103-08 whose baseline WBC cystine levels were much higher than most of other subjects and those enrolled in RP103-03 (See Section 3.4.4.1).

3.4 Reviewer's Analyses

3.4.1 Introduction

The applicant's PK-PD analyses comparing pediatric patients <6 years of age and those older than 6 years were performed based on the data obtained from RP103-03 and RP103-08. Since RP103-04 also included relevant information for pediatric PK-PD, the reviewer conducted additional analysis to compared PK-PD using data from RP103-04 as well as a subgroup analysis for age group for Study RP103-08.

3.4.2 Objectives

- To compare PK-PD in pediatric patients <6 years of age and that in patients ≥6 years of age
- To compare PK-PD in pediatric patients <2 years of age and that in patients ≥2 years of age

3.4.3 Datasets

Datasets utilized for the analyses are summarized in Table 6.

Table 6. Analysis Data Sets

Study Number	Name	Link to EDR
RP103-03 RP103-04	Adpk.xpt Adpd.xpt Adex.xpt	//cdsesub1/evsprod/NDA203389/0073/m5/datasets/ise/analysis/adam
RP103-08	Adpk.xpt Adpd.xpt Adex.xpt	//CDSESUB1/evsprod/NDA203389//0108/m5/datasets/rp103-08/analysis/adam

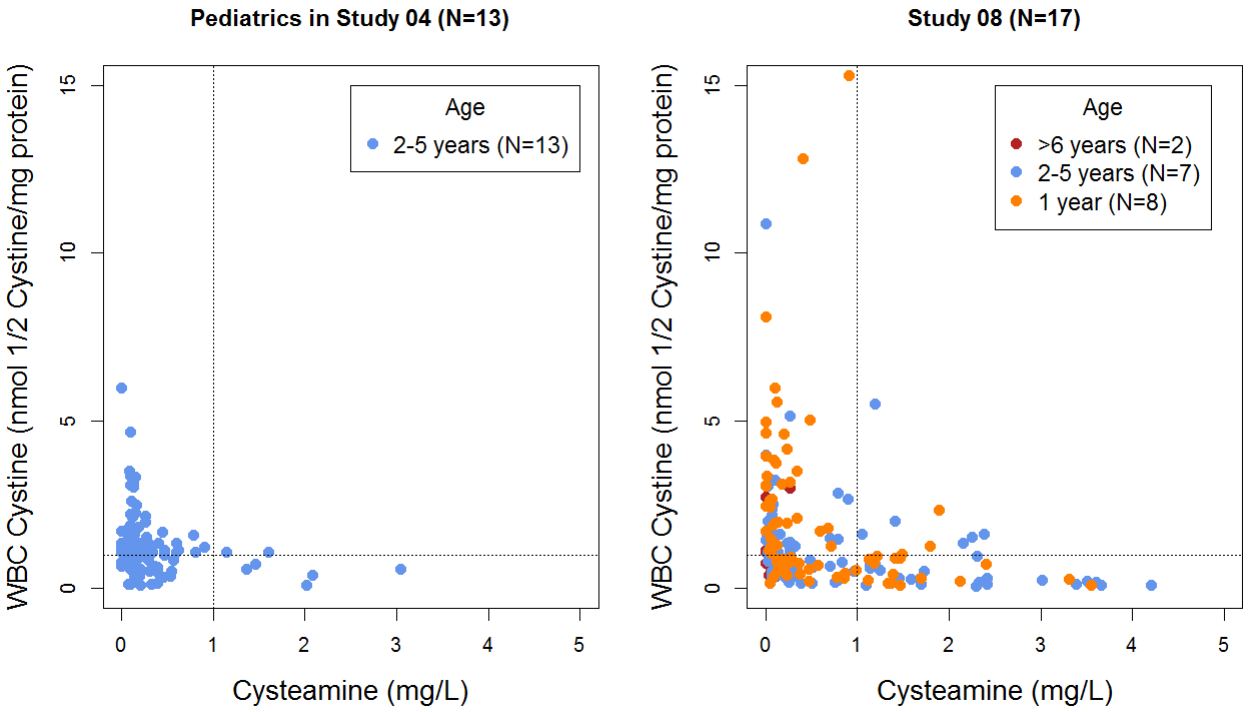
3.4.4 Results

3.4.4.1 Exposure-Response Analyses Using 30-Min Post-dose WBC Cystine in Children <6 Years

The exposure-response analysis for WBC cystine at 30-minutes post-dose in children 2-5 years of age from Study RP103-08 was performed and compared to that in children <6 years from Study RP103-04 (who were newly enrolled to Study RP103-04 while older children and adults were continuing from Study RP103-03). As shown in ls.

Figure 9, it appeared that multiple subjects, particularly those 1 year old, in RP103-08 might have under-dosed resulting in lower cysteamine concentrations and higher WBC cystine levels.

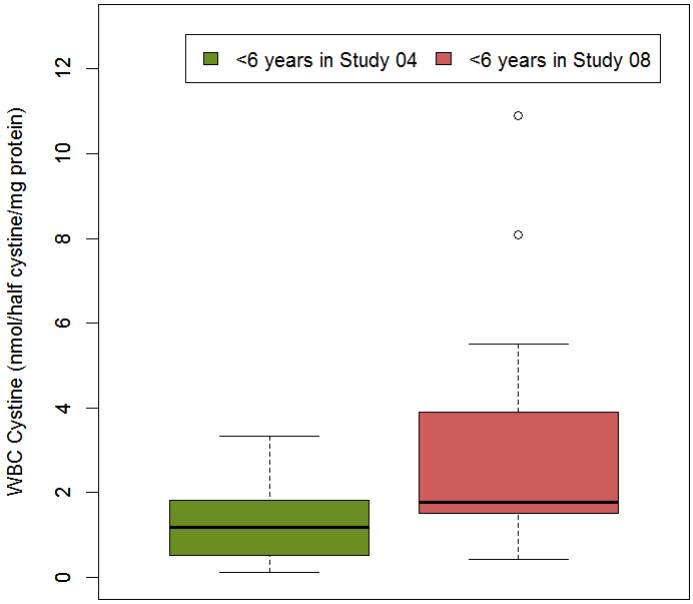
Figure 9. Comparison of Exposure-Response Relationship between Children <6 Years in Study RP103-04 and Children <6 Years in Study RP103-08 with 30-Minute Post-Dose Cysteamine and 30-Minute Post-dose WBC Cystine



(Source: Reviewer's anlaysis, subjects <6 years from Study RP103-04 and all subjects enrolled in Study RP103-08 were included in the analysis regardless of baseline WBC cystine level)

By comparing baseline WBC cystine levels between these two groups of patients, the review team concluded that high levels of baseline WBC might be associated with lower response to Procysbi®. As shown in Figure 10, there was a significant difference in baseline WBC cystine between subjects in RP103-04 and those in RP103-08. Three subjects whose baseline WBC cystine level was above 4 nmol/half cystine/mg protein and all of them were below 6 years of age.

Figure 10. Comparison of WBC Cystine on Day 1 between Children <6 Years in Study RP103-04 and Children <6 Years in Study RP103-08



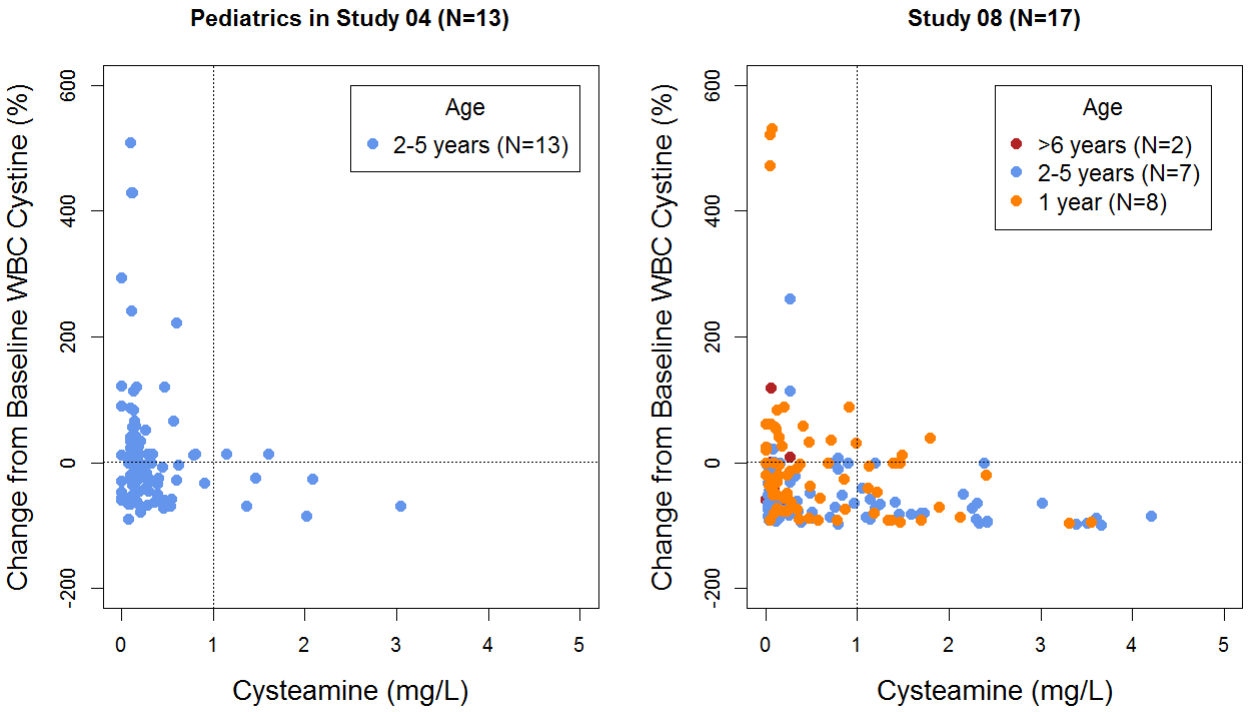
(Source: Reviewer's analysis)

Thus, the comparison of exposure-response relationship was made only for children whose baseline WBC cystine was below 4 nmol/half cystine/mg protein, which was slightly greater than the maximum baseline WBC cystine (3.3 nmol/half cystine/mg protein) observed children <6 years in Study RP103-04. As shown in Figure 2, exposure-response relationship between these two groups of patients became comparable.

3.4.4.2 Exposure-Response Analyses Using Percent Change from Baseline WBC Cystine

As a confirmatory analysis, another exposure-response analysis was performed using percent change from baseline WBC cystine, including those subjects with high baseline WBC cystine. As shown in Figure 11, the relationship between cysteamine concentration and %change from baseline WBC cystine for children <6 years in Study RP103-04 and that ER for all subjects in Study RP103-08 including 1-year old children, were similar.

Figure 11. Comparison of Exposure-Response Relationship between Children <6 Years in Study RP103-03 and Children <6 Years in Study RP103-08 with 30-Minute Post-Dose Cysteamine and Change from Baseline WBC Cystine



(Source: Reviewer's anlaysis, subjects <6 years from Study RP103-03 and all subjects enrolled in Study RP103-08 were included in the analysis regardless of baseline WBC cystine level)

3.4.4.3 Comparison of PK-PD by Age Group (Children ≥6 Years and Adults versus Children<6 Years)

PK-PD of Procysbi® was compared between subjects <6 years of age in RP103-08 and subjects ≥6 years of age in RP103-04 using cysteamine concentrations at 30-minute post-dose and WBC cystine levels at 30-minute post-dose data up to Month 18. Among subjects enrolled in Study RP103-04, subjects who were previously treated with either Cystagon® or Procysbi® in Study RP103-03 (N=40) and newly enrolled subjects after renal transplantation (N=6) who were treated with Cystagon® at Screening were included in the analysis. As shown in Figure 1, both PK and PD profiles over time are overall comparable between these two populations.

3.4.4.4 Comparison of PK-PD by Age Group (Children ≥2 Years versus Children <2 Years)

To compare PK-PD between children ≥2 years of age and <2 years of age (all were 1 year old), PK-PD profiles over time were generated. As shown in Figure 3, they were comparable. Nonetheless, it

is difficult to make a clear conclusion for difference due to small sample size and other confounding effects, such as route of administration.

3.5 Analytical Section

3.5.1 How was cysteamine concentration measured in the plasma and cystine and total protein in human white blood cell lysate were measured?

Cysteamine in human plasma and cystine in white blood cell lysate obtained from Study RP103-08 were measured by validated LC/MS/MS, the similar methods utilized for previous studies (RP103-03 & RP103-04). In addition, protein concentration was measured by bicinchoninic acid (BCA) protein assay using commercially available assay kit.

However, the blood samples for Study RP103-08 were analyzed by two individual CRO, (b) (4) and (b) (4) The blood samples for cysteamine and WBC cystine collected before August 2014 were analyzed by (b) (4) while the samples collected after August 2014 were analyzed by (b) (4) (Table 7). Although the bioanalytical methods were validated in both of CROs, the calibration ranges for cysteamine, cystine and protein concentration were different. The summary and comparison of bioanalytical methods for cysteamine, cystine and protein assays from two CROs were listed as follows (Tables 8-10):

Table 7. Analytical site for blood samples from individual subjects

17 subjects (subject ID)	(b) (4)	(b) (4)
01008	All samples	
01009	First 11 samples ("Day 1" through "Quarterly 4" visits)	Last 2 samples ("Quarterly 5" and "Study Exit" visits)
01010	First 9 samples ("Day 1" through "Quarterly 2" visits)	Last 2 samples ("Quarterly 3" and "Study Exit" visits)
01011, 01012, 01013, 21001, 21002, 21003, 21004, 21005, 21006, 21007, 21008, 21009, 21010, and 21011		All samples

Table 8. Validation LC-MS/MS Bioanalytical Method for the Analysis of Cysteamine in Human Plasma

	Criteria Guidance	(b) (4)	(b) (4)
Matrix		Human Plasma	Human Plasma
Storage Sample Temperature		-70°C	-70°C
Sample Volume		25 uL	25 uL

Standard Calibrator Range	6 concentrations in duplicates	75.0 to 10000 ng/mL	10.0 to 2500 ng/mL
QC Samples		200.0, 4000, 7500 ng/mL	30.0, 500, 2000 ng/mL
Precision	Within batch CV < 15% (<20% for LLOQ)	1 to 3%	1.4 to 4.8%
Accuracy	Within batch RE < 15% (<20% for LLOQ)	-4.8 to 2.3%	-5.7 to 0.6%
Dilution Factor	Human WBC Lysates	50	10

Table 9. Validation LC-MS/MS Bioanalytical Method for the Analysis of Cystine in Human White Blood Cell (WBC) Lysate

	Criteria Guidance	(b) (4)	(b) (4)
Matrix		Human WBC Lysates	Human WBC Lysates
Storage Sample Temperature		-70°C	-70°C
Sample Volume		50 uL	50 uL
Standard Calibrator Range	6 concentrations in duplicate	3.00 to 1130 ng/mL	4.00 to 1500 ng/mL
QC Samples		9.00, 450, 900 ng/mL	12.0, 300, 1200 ng/mL
Precision	Within batch CV < 15% (<20% for LLOQ)	1.9 to 6.4%	1.3 to 8.3%
Accuracy	Within batch RE < 15% (<20% for LLOQ)	-6.3 to 8.4%	-7.8 to 4.0%
Dilution Factor	Human WBC Lysates	10	10

Table 10. Validation of Total Protein Content Method

	Criteria Guidance	(b) (4)	(b) (4)
Kit		Pierce BCA Kit	Pierce BCA Kit
Matrix		Human WBC Lysates	Human WBC Lysates
Storage Sample Temperature		-70°C	-70°C
Standard Calibrator Range		25 to 2,000 ug/mL	37.5 to 2000 ug/mL
Standard Calibrator Precision	Min 75% of the SC within 20% of nominal concentration except LLOQ+/- 25%	-2 to 1.6%	-0.8 to 1.2%
R-squared	>0.970	0.999	0.9995
QC Samples		75, 300, 800, and 1600 ug/mL	37.5, 113, 800, 1600 and 2000 ug/mL
Replicate Precision	Within 20%	0.8 to 3.2%	1.1 to 13.9%
QC Samples Performance	Within 20% for at least 50% at each concentration	-6.5 to 0.6%	5.4 to 16.9%
Dilution Factor	RE < 20%	10	45.6

RE = Relative Error

Reviewer's comments: The bioanalytical methods were validated methods, but we requested the applicant to conduct cross-validation for methods from (b) (4) *and* (b) (4) *The response to IR were received on October 26th, 2017 and Nov 3rd, 2017, the applicant presented the table, raw data and analyzed subject ID of cross-validation for cysteamine, cystine and protein content assay, shown as follows:*

Table 11. Comparability of cysteamine, cystine and total protein content assay results from same samples tested at (b) (4) **and** (b) (4)

Sample	Measured Cysteamine Concentration (ng/mL)		Measured Cystine Concentration (ng/mL)		Measured Total Protein Content (mg/mL)		Calculated WBC Cystine Concentration (nmol half cystine/mg protein)	
	(b) (4)							
1	4620	4120	6.96	6.14	468	420	0.0583	0.0571
2	1830	1770	25.9	27.2	1380	1330	0.049	0.0533
3	273	277	13.8	13.4	3420	3240	0.0317	0.0323
4	973	901	16.8	18.0	3380	3040	0.0388	0.0464
5	1770	1530	14.9	62.6	1980	2080	0.059	0.235
6	504	491	4.17	16.5	3030	2670	0.0108	0.0486
7	187	182	579	554	1240	1020	3.66	4.25
8	97.3	106	596	524	1390	1030	3.35	3.97
9	95.1	103	684	579	1740	2760	3.09	1.65
10	4090	4430	30.3	31.2	2650	2140	0.0299	0.0381
Coefficient of Determination (R^2)	0.98		0.99		0.82		0.89	

Reviewer's comments: The cross-validation was done using ten samples from study RP103-04 instead of current study RP103-08. But the raw data and calculation results were generally comparable between two methods from (b) (4) *and* (b) (4) *and the cysteamine, cystine and protein concentration could be compared. It is noted that measured cystine concentrations in two samples (#5 and 6 in Table 9) out of ten samples >20% differed between two methods. The cross-validation results indicated that the comparison between measured concentrations of cysteamine, cystine and protein content by two laboratories is appropriate.*

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/s/

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