U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	203-389
Supplement #:	020
Drug Name:	Procysbi (cysteamine bitartrate) 25mg and 75mg Oral Capsules
Indication(s):	Treatment of nephropathic cystinosis in children less than 6 years old
Applicant:	Horizon Pharma USA, Inc.
Date(s):	Submit Date: June 29, 2017
	PDUFA Due Date: December 15, 2017
Review Priority:	Priority
Biometrics Division:	Division of Biometrics III
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Keywords: clinical studies, NDA review, open-label

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1 EXECUTIVE SUMMARY

The sponsor submitted a single-arm study for cysteamine bitartrate delayed-release oral capsules (25mg and 75mg) as a post-marketing commitment for the treatment of nephropathic cystinosis subjects aged birth to less than 6 years who were naïve to cysteamine treatment.

The primary objective of the study was to assess the effectiveness and safety of long-term, repeat dosing of cysteamine bitrartrate on white blood cell (WBC) cystine levels in cystinosis subjects who were cysteamine treatment naïve through the primary efficacy endpoint, the steady-state cysteamine-trough WBC cystine level 30 minutes post dose at each study visit.

The two secondary efficacy endpoints were standing height and standing weight growth as measured using standardized norms for growth based on age.

After thorough evaluation, we confirmed that the cysteamine bitartrate arm indeed demonstrated a decrease in mean WBC cystine levels and an increase in mean height and weight during the study's treatment period. However, given the occurrence of incomplete WBC cystine level data, whether the observed decreases in WBC cystine levels, and the observed height and weight increases were clinically meaningful will be determined by the clinical review team. Additionally, since this study was open-label with a single test drug, this study's findings should be interpreted with caution due to the absence of a concurrent comparator and proper blinding.

2 INTRODUCTION

2.1 Overview

The sponsor submitted a phase 3b study (Study RP103-08) of the delayed-release formulation of cysteamine bitartrate to address the FDA's written request for pharmacokinetic (PK)/pharmacodynamic (PD), safety, and efficacy data on cysteamine bitartrate treatment in children aged less than 6 years.

Cysteamine bitartrate delayed-release capsules were initially approved by the FDA on April 30, 2013, for the management of nephropathic cystinosis in adults and children aged 6 years and older. The use of cysteamine bitartrate in children aged between 2 to 6 years with nephropathic cystinosis was approved on August 14, 2015. The FDA issued a formal written request dated August 19, 2013, and amended on October 6, 2015, for the sponsor to conduct a one-year, open-label, PK/PD, safety and efficacy study in pediatric subjects with nephropathic cystinosis aged birth to less than 6 years.

Study RP103-08 was a long-term (at least 12 weeks), open-label study designed to assess the effectiveness and safety of long-term, repeat dosing of cysteamine bitartrate in pediatric nephropathic cystinosis subjects aged birth to less than 6 years who were cysteamine treatment naïve. The study also evaluated a new treatment initiation and titration methodology designed to maximize tolerability of cysteamine bitartrate in treatment-naïve subjects.

2.2 Data Sources

The clinical study report (CSR), protocol, statistical analysis plan (SAP), Statistical Analysis System (SAS) transport datasets in Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) format, SAS codes, and dataset reviewer's guides for the study were submitted electronically.

The network path for the submission is \\cdsesub1\evsprod\NDA203389\0108\m5\53-clin-stud-rep\535-rep-effic-safety-stud\cystinosis\5352-stud-rep-uncontr . The network path for the analysis datasets is \\cdsesub1\evsprod\NDA203389\0108\m5\datasets .

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the data submitted by the sponsor to support the effectiveness and safety of cysteamine bitartrate for the proposed indication were acceptable.

3.2 Evaluation of Efficacy

One CSR for Study RP103-08 was included for demonstrating the effectiveness and safety of cysteamine bitartrate 25mg and 75mg oral capsules for the treatment of nephropathic cystinosis

in pediatric subjects aged birth to less than 6 years. Study RP103-08 was conducted at one site in the United States (US) and another site in Brazil.

3.2.1 Study Design and Endpoints

Study RP103-08 was a long-term, open-label study whose primary objective was to assess the effectiveness and safety of long-term, repeat dosing of cysteamine bitartrate delayed-release capsules on WBC cystine levels in cystinosis subjects who were cysteamine treatment naïve. The study also evaluated a new treatment initiation and titration methodology for maximizing tolerability of cysteamine bitartrate in treatment-naïve subjects.

As of Protocol Amendment 1, dated July 24, 2014, the study assessed steady-state cysteamine PK/PD in children less than 6 years old. Subjects were to receive cysteamine bitartrate treatment for at least 12 months.

Enrollment Criteria
The main inclusion criteria that defined the study population were as follows:

1) A documented diagnosis of cystinosis
2) No clinically significant change in liver function tests, i.e. 1.5 times upper limit of normal (ULN) for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and/or 1.5 times ULN for total bilirubin, within 6 months prior to Screening
3) No clinically significant change in renal function, i.e. estimated glomerular filtration rate (GFR) within 6 months prior to Screening
4) Must have an estimated GFR > 20 mL/minute/1.73 m^2
5) Has not taken any form of cysteamine bitartrate in the past
6) Less than 6 years of age.

Treatment and Randomization
The study was open-label with a single test drug, so no randomization was performed. The study drug's starting dose was based on the subject's age, weight, and body surface area (BSA). The dose was to be gradually escalated (10% steps, every 2 weeks) until the subject's WBC cystine level was < 1 nmol ½ cystine/mg protein. Dose reduction and/or a more gradual dose escalation could have been considered for tolerability reasons.

The Primary Efficacy Endpoint was the steady-state cysteamine-trough WBC cystine level 30 minutes post dose at each study visit.

The Secondary Efficacy Endpoints were standing height and standing weight growth as measured using standardized norms for growth based on age.

3.2.2 Statistical Methodologies

Analysis Population

Statistical analyses of the primary and secondary efficacy endpoints utilized the PD Population, which was defined as all subjects who received at least one dose of study drug and who had at least one WBC cystine level measurement.

Analysis of the Primary Endpoint
The primary endpoint of WBC cystine levels 30 minutes post dose at each study visit was summarized using descriptive statistics on a linear scale and a log scale (number of subjects, mean, geometric mean [GM], coefficient of variation [CV], median, standard deviation [SD], minimum, and maximum). The CSR included summaries for the observed value, change from baseline at month 6, percent change from baseline at month 6, and proportion of subjects who reached a WBC cystine level < 1.0 nmol ½ cystine/mg protein at each visit.

Analysis of the Secondary Endpoints
The secondary endpoints of standing height and standing weight growth as measured using standardized norms for growth based on age were summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum). The CSR included summaries for the observed value, change from baseline, and percent change from baseline at each visit for height and weight, as well as for body mass index (BMI) and BSA. The height and weight z-scores were based on Centers for Disease Control and Prevention (CDC) growth data of the general population.

Multiple Testing Approach
No formal multiplicity adjustment was planned for this exploratory study with a descriptive interpretation.

Handling of Missing Data
No substitutions were made to accommodate missing data.

Sample Size Planned
The protocol specified that approximately 20 cysteamine naïve subjects with cystinosis were to be enrolled in the study with a target of 12 subjects under 6 years of age at the time of screening. No formal sample size assessment was made.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition
As noted previously, Study RP103-08 was conducted at one site in the US and another site in Brazil. Although 20 subjects were originally planned, only 17 subjects were screened, enrolled, and treated. Of those 17 subjects, six subjects (35.3%) were enrolled from the US, and 11 subjects (64.7%) were enrolled from Brazil. Sixteen subjects (94.1%) completed the study: 14 subjects completed at least 12 months of treatment, 1 subject completed 355 days of treatment, and 1 subject completed 358 days of treatment. One subject (5.9%) withdrew from the study early due to death.

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

- ≥ 6 years old: 2 subjects
- < 6 years old: 15 subjects
- < 2 years old: 7 subjects
- ≥ 2 years old: 10 subjects
- ≥ 2 and < 6 years old: 8 subjects

Subject disposition for all subjects is summarized in Table 1.

Table 1. Subject Disposition

Characteristic	All Subjects (N=17)
Screened[1]	17
Enrolled[2]	17
Treated	17
Completed	16 (94.1%)
Discontinued	1 (5.9%)

[1] Signed informed consent.
[2] The number of subjects with a Day 1 visit.
Source: CSR Table 10-1 (p. 62)

Demographic and Baseline Characteristics

Demographic and baseline characteristics for the age < 6 years subgroup are summarized in Table 2. Among the 15 subjects who were < 6 years old, 8 subjects (53.3%) were male, 11 subjects (73.3%) were white, and 8 subjects (53.3%) were ≥ 2 years old. The mean (± SD) age was 2.22 ± 0.985 years, with a range of 1.04 to 4.53 years. The mean weight was 9.01 ± 2.015 kg, and the mean height was 77.12 ± 7.505 cm.

Table 2. Demographic and Baseline Characteristics

Characteristic	Subjects Age < 6 Years (N=15)
Age (years)	
n	15
Mean (SD)	2.22 (0.985)
Median	2.28
Min, Max	1.04, 4.53
Age Subgroups, n (%)	
n	
< 2 years	7 (46.7)
≥ 2 years	8 (53.3)
Gender, n (%)	
Male	8 (53.3)
Female	7 (46.7)
Race, n (%)	
American Indian or Alaska Native	0
Asian	0
Black	4 (26.7)
Native Hawaiian or Other Pacific Islander	0

White	11 (73.3)
Other	0
Ethnicity, n (%)	
Hispanic or Latino	11 (73.3)
Not Hispanic or Latino	4 (26.7)
Weight (kg)	
n	15
Mean (SD)	9.01 (2.015)
Median	9.30
Min, Max	5.80, 13.20
Height (cm)	
n	15
Mean (SD)	77.12 (7.505)
Median	79.30
Min, Max	62.30, 86.10
BMI (kg/m^2)	
n	15
Mean (SD)	14.98 (1.258)
Median	14.84
Min, Max	13.39, 17.93
BSA (m^2)	
n	15
Mean (SD)	0.44 (0.070)
Median	0.45
Min, Max	0.32, 0.57

Source: CSR Table 11-2 (p. 67-69)

3.2.4 Efficacy Results and Conclusions

3.2.4.1 Primary Efficacy Endpoint: Steady-state Cysteamine-trough WBC Cystine Level 30 Minutes Post Dose at Each Study Visit

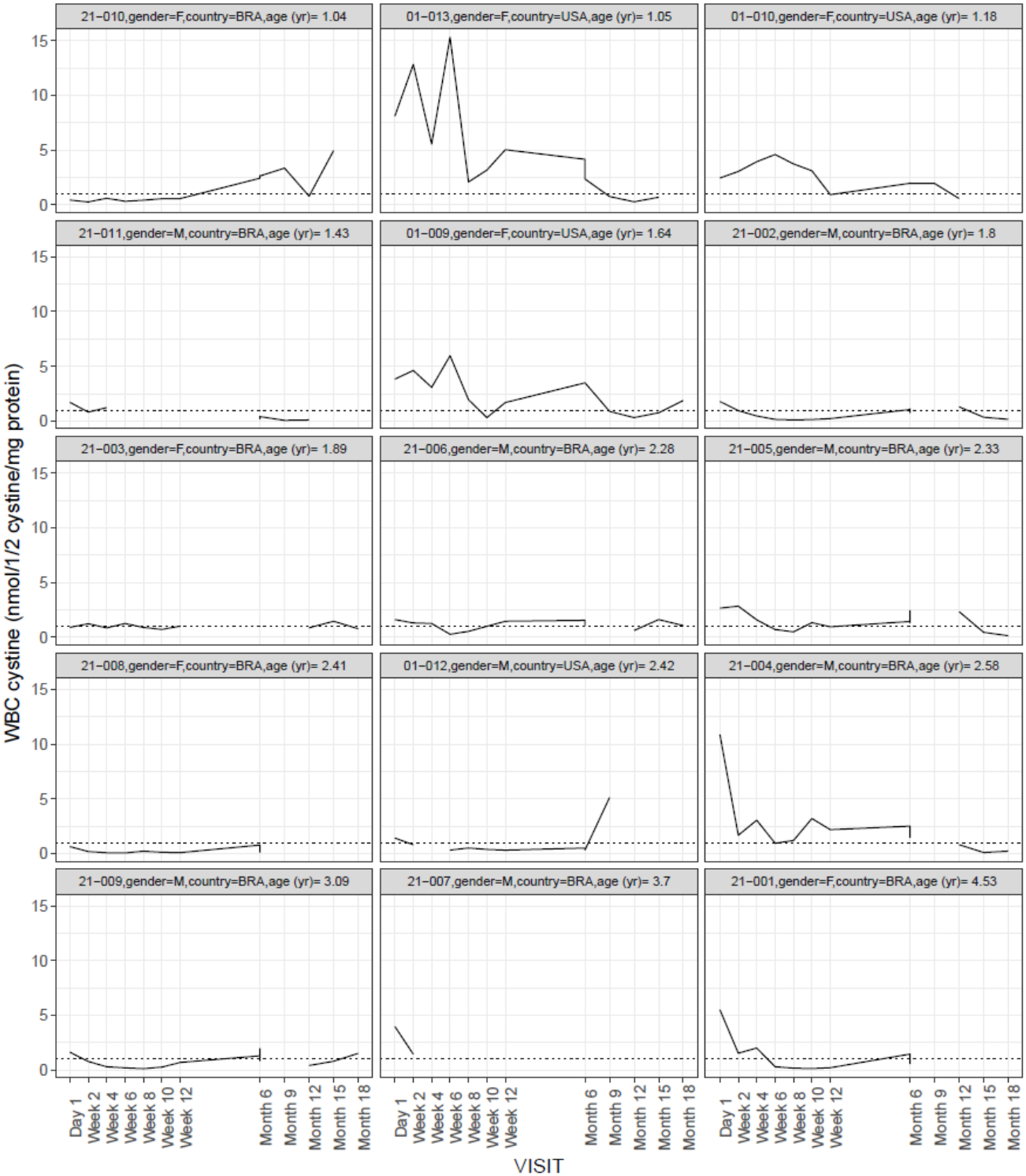
The sponsor's results for the primary efficacy endpoint based on the PD Population are displayed in Table 3. There was a decrease in mean (± SD) WBC cystine level during the study's treatment period, from 3.2 ± 2.95 to 0.8 ± 0.76 nmol ½ cystine/mg protein at Day 1 and Study Exit, respectively. Although the mean WBC cystine levels decreased during the study, not all subjects had available WBC cystine level data at each visit, as shown in Figure 1. The numbers of subjects with WBC cystine level data varied as the study progressed, from 15 subjects at Day 1, 2 subjects at Month 6, 6 subjects at Month 9, 13 subjects at Month 12, and 13 subjects at Study Exit. These results were confirmed by the statistical reviewer. WBC cystine levels at 30 minutes post dose for all subjects, as well as a linear regression line representing the WBC cystine levels regressed on study visit, are displayed in Figure 2. The linear regression results indicate a decreasing trend in WBC cystine level over time.

Table 3. Sponsor's Results of WBC Cystine Level 30 Minutes Post Dose at Each Study Visit

Subjects Age < 6 Years (N=15)	Statistics	Linear Scale nmol ½ cystine/mg protein
Day 1 (N=15)	Mean (SD)	3.1709 (2.95209)
	Median	1.7843
	Min, Max	0.423, 10.888
Week 2 (N=15)	Mean (SD)	2.2899 (3.13707)
	Median	1.3153
	Min, Max	0.192, 12.816
Week 4 (N=13)	Mean (SD)	1.8474 (1.62820)
	Median	1.2648
	Min, Max	0.087, 5.549
Week 6 (N=13)	Mean (SD)	2.3403 (4.31136)
	Median	0.3258
	Min, Max	0.067, 15.300
Week 8 (N=13)	Mean (SD)	0.9589 (1.05851)
	Median	0.5182
	Min, Max	0.103, 3.730
Week 10 (N=12)	Mean (SD)	1.1219 (1.27413)
	Median	0.4693
	Min, Max	0.128, 3.213
Week 12 (N=13)	Mean (SD)	1.1828 (1.31272)
	Median	0.9200
	Min, Max	0.095, 5.024
Month 6 (N=2)	Mean (SD)	2.7250 (1.08187)
	Median	2.7250
	Min, Max	1.960, 3.490
Month 9 (N=6)	Mean (SD)	2.0196 (1.90931)
	Median	1.4105
	Min, Max	0.063, 5.139
Month 12 (N=13)	Mean (SD)	0.8012 (0.59706)
	Median	0.6345
	Min, Max	0.098, 2.350
Month 15 (N=9)	Mean (SD)	1.2443 (1.47616)
	Median	0.7590
	Min, Max	0.105, 4.954
Month 18 (N=9)	Mean (SD)	0.7356 (0.64027)
	Median	0.6420
	Min, Max	0.150, 1.875
Study Exit (N=13)	Mean (SD)	0.8197 (0.76413)
	Median	0.4946
	Min, Max	0.252, 2.945

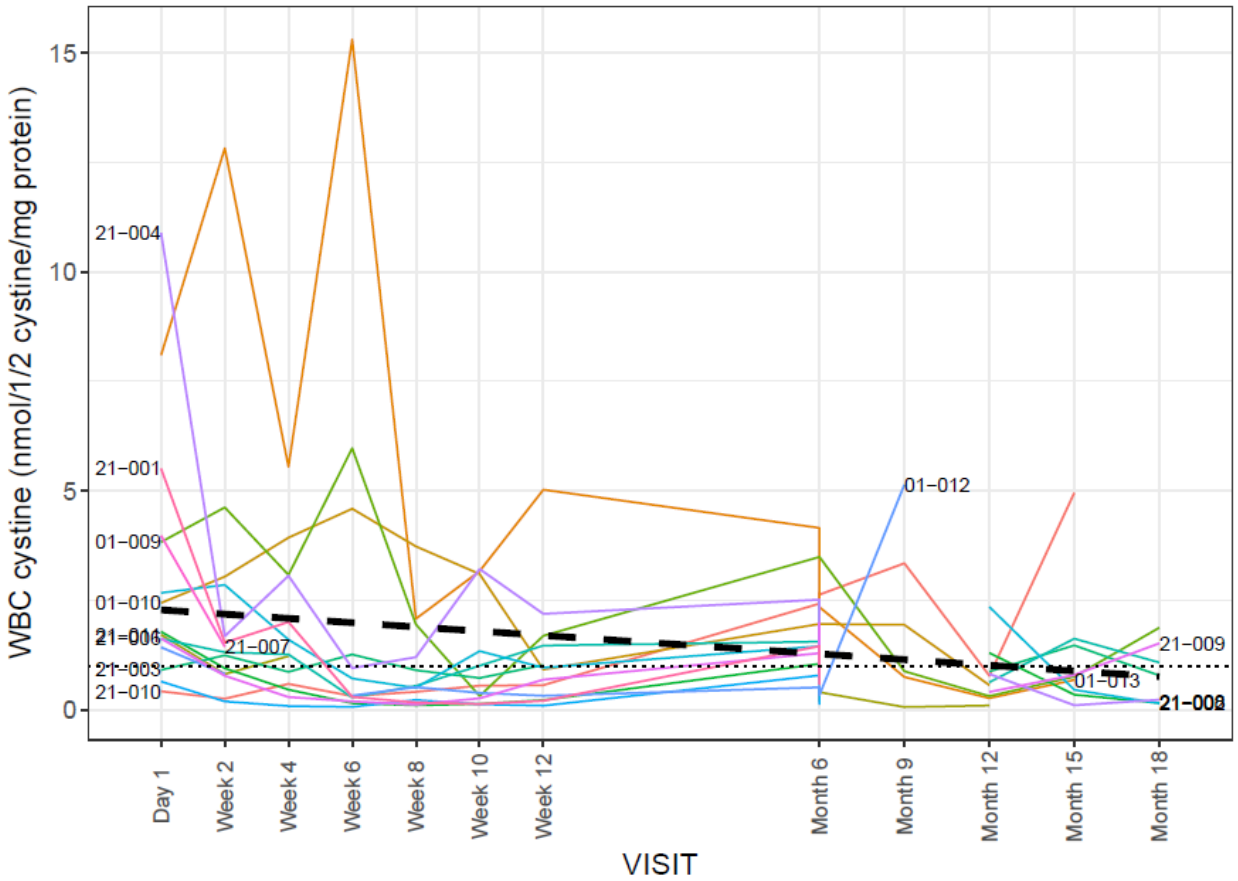
Source: CSR Table 11-5 (p. 75-77)

Figure 1. WBC Cystine Level 30 Minutes Post Dose at Each Study Visit by Subject



Note: M=male. F=female. BRA=Brazil. The dotted line displayed for each subject represents a reference line at y=1.
Source: Statistical reviewer's analysis, PD Population

Figure 2. Overall WBC Cystine Level 30 Minutes Post Dose at Each Study Visit



Note: The dotted line represents a reference line at y=1. The dashed line represents a linear regression of WBC cystine level regressed on visit.
Source: Statistical reviewer's analysis, PD Population

The percentage of subjects who reached WBC cystine < 1.0 nmol ½ cystine/mg protein after the start of treatment increased during the study's treatment period, from 6/15 (40.0%) at Week 2 to 8/13 (61.5%) at Week 12, and 10/13 (76.9%) at Study Exit (Table 4). Although the sponsor reported that those percentages of subjects increased progressively over the study's treatment period, the percentages did not show this progressive increase (Table 4). Additionally, not all subjects had available WBC cystine level data at each visit, and subjects with a WBC cystine level < 1 nmol ½ cystine/mg protein at a particular visit may not have had the WBC cystine level remain < 1 nmol ½ cystine/mg protein at subsequent visits, as shown in Figure 1.

Table 4. Sponsor's Results of Percentage of Subjects who Reached WBC Cystine Level < 1.0 nmol ½ cystine/mg protein at Each Study Visit

Visit		Subjects Age < 6 Years (N = 15) n (%)
Day 1	(n=15)	3 (20.0)
Week 2	(n=15)	6 (40.0)
Week 4	(n=13)	5 (38.5)
Week 6	(n=13)	9 (69.2)
Week 8	(n=13)	9 (69.2)
Week 10	(n=12)	8 (66.7)
Week 12	(n=13)	8 (61.5)
Month 6 (all time points)	(n=13)	6 (46.2)
Month 9	(n=6)	3 (50.0)
Month 12	(n=13)	10 (76.9)
Month 15	(n=9)	6 (66.7)
Month 18	(n=9)	6 (66.7)
Study Exit	(n=13)	10 (76.9)

Source: CSR Table 11-7 (p. 80)

3.2.4.2 Secondary Efficacy Endpoints: Standing Height and Standing Weight Growth Using Standardized Norms for Growth Based on Age

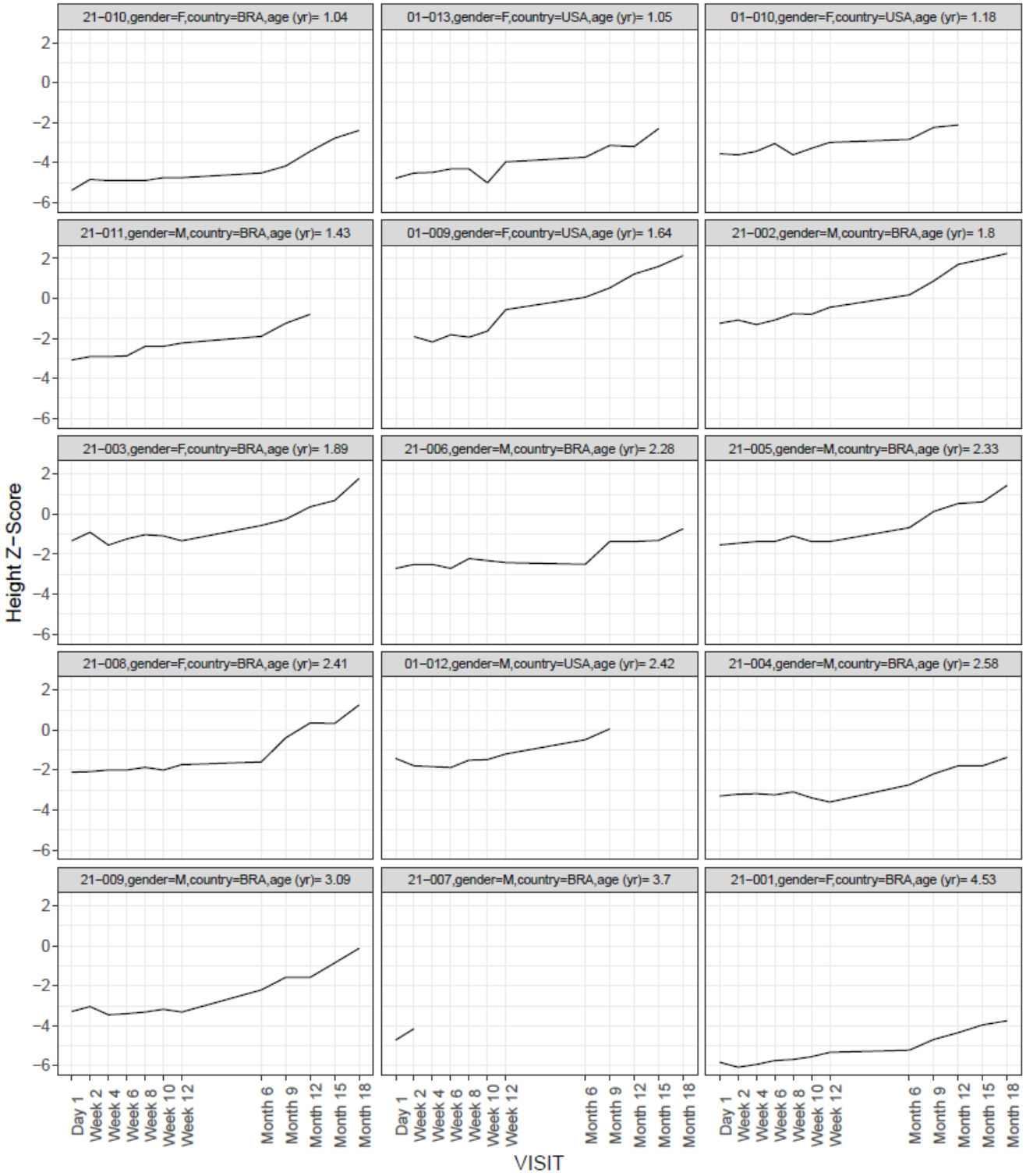
The sponsor's results for the secondary efficacy endpoints of standing height and standing weight growth using standardized norms for growth based on age are displayed in Table 5 and Table 6, respectively. There was an increase in mean height and weight during the study's treatment period. The mean z-scores for height, based on CDC growth charts as a reference population, were negative values from Day 1 through Month 15, and were positive values thereafter. The mean (± SD) height z-scores were -3.16 ± 1.55 at Day 1 and 0.11 ± 1.96 at Study Exit. The mean z-scores for weight, based on CDC growth charts as a reference population, were negative values that decreased in absolute value during the study. The mean (± SD) weight z-scores were -3.98 ± 2.07 at Day 1 and -1.10 ± 1.78 at Study Exit. These results were confirmed by the statistical reviewer. Subject-level height and weight z-scores are displayed in Figure 2 and Figure 3, respectively. Height and weight z-scores for all subjects, as well as a linear regression line representing the height and weight z-scores regressed on study visit, are displayed in Figure 4 and Figure 5, respectively. The linear regression results indicate an increasing trend in height and weight z-scores over time.

Table 5. Sponsor's Results of Standing Height Growth Using Standardized Norms for Growth Based on Age

Subjects Age < 6 Years (N=15)	Statistics	Z-score
Day 1 (N=14)	Mean (SD)	-3.16 (1.55)
	Median	-3.18
	Min, Max	-5.82, -1.24
Week 2 (N=15)	Mean (SD)	-2.94 (1.49)
	Median	-2.91
	Min, Max	-6.07, -0.90
Week 4 (N=13)	Mean (SD)	-3.02 (1.43)
	Median	-2.91
	Min, Max	-5.93, -1.31
Week 6 (N=14)	Mean (SD)	-2.83 (1.41)
	Median	-2.79
	Min, Max	-5.74, -1.08
Week 8 (N=14)	Mean (SD)	-2.69 (1.52)
	Median	-2.31
	Min, Max	-5.69, -0.76
Week 10 (N=13)	Mean (SD)	-2.76 (1.58)
	Median	-2.40
	Min, Max	-5.55, -0.79
Week 12 (N=14)	Mean (SD)	-2.52 (1.53)
	Median	-2.33
	Min, Max	-5.33, -0.44
Month 6 (N=14)	Mean (SD)	-2.05 (1.68)
	Median	-2.05
	Min, Max	-5.22, 0.18
Month 9 (N=14)	Mean (SD)	-1.40 (1.72)
	Median	-1.30
	Min, Max	-4.69, 0.88
Month 12 (N=13)	Mean (SD)	-1.11 (1.88)
	Median	-1.37
	Min, Max	-4.34, 1.70
Month 15 (N=11)	Mean (SD)	-0.71 (1.90)
	Median	-0.85
	Min, Max	-3.95, 1.97
Month 18 (N=10)	Mean (SD)	0.05 (2.07)
	Median	0.57
	Min, Max	-3.75, 2.25
Study Exit (N=14)	Mean (SD)	0.11 (1.96)
	Median	-0.28
	Min, Max	-3.83, 3.08

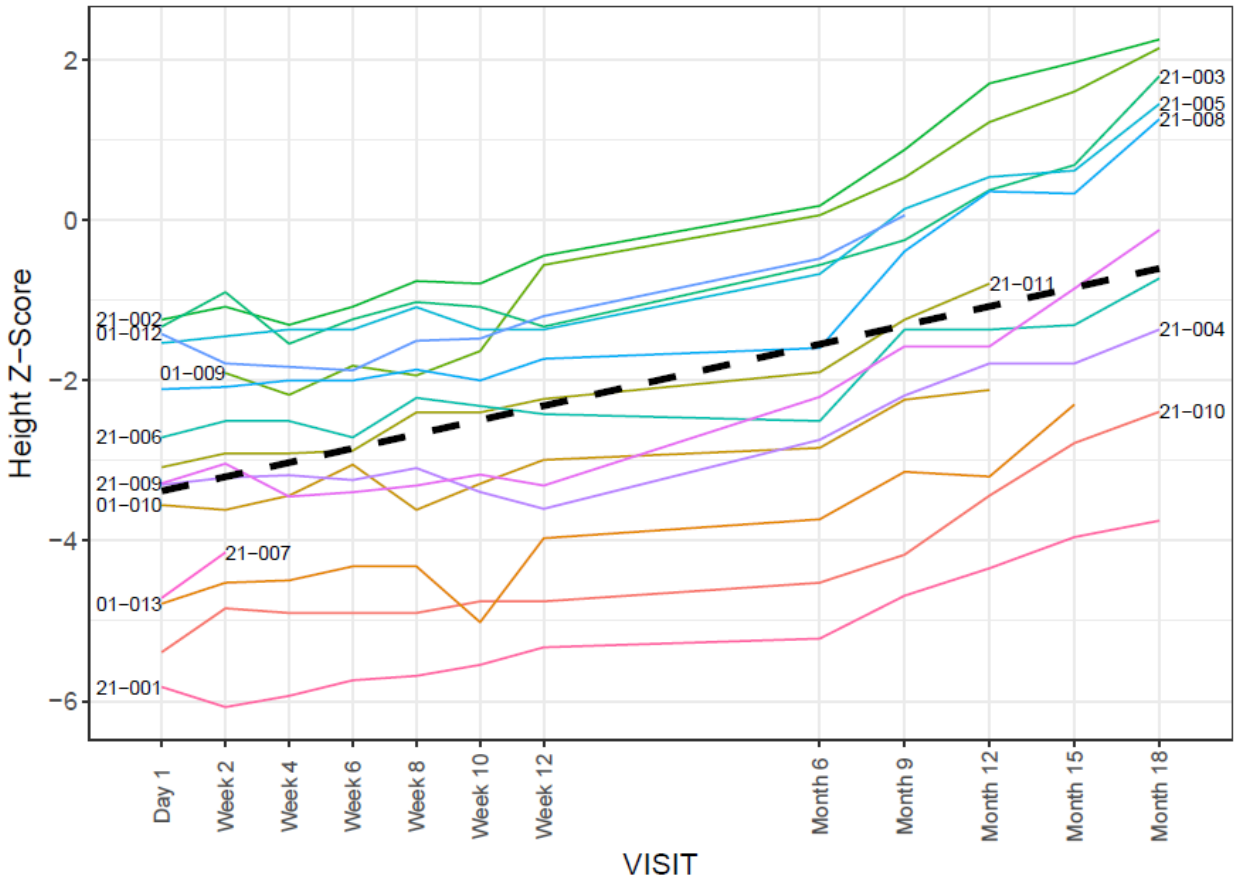
Source: CSR Table 11-8 (p. 81-82)

Figure 3. Standing Height Using Standardized Norms for Growth Based on Age by Subject



Note: M=male. F=female. BRA=Brazil.
Source: Statistical reviewer's analysis, PD Population

Figure 4. Overall Standing Height Using Standardized Norms for Growth Based on Age



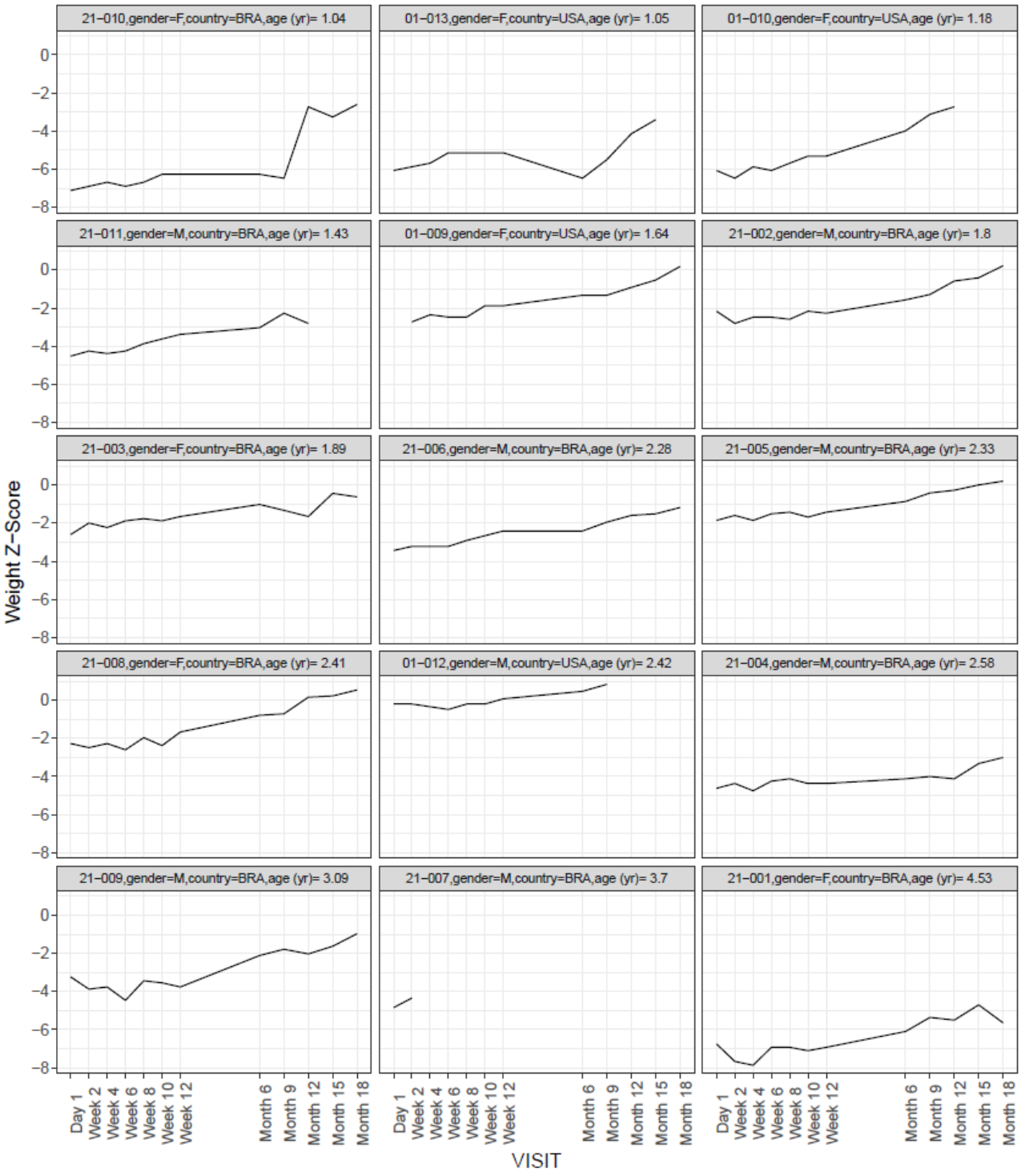
Note: The dashed line represents a linear regression of height z-score regressed on visit.
Source: Statistical reviewer's analysis, PD Population

Table 6. Sponsor's Results of Standing Weight Growth Using Standardized Norms for Growth Based on Age

Subjects Age < 6 Years (N=15)	Statistics	Z-score
Day 1 (N=14)	Mean (SD)	-3.98 (2.07)
	Median	-3.98
	Min, Max	-7.12, -0.20
Week 2 (N=15)	Mean (SD)	-3.92 (2.10)
	Median	-3.87
	Min, Max	-7.67, -0.20
Week 4 (N=13)	Mean (SD)	-4.11 (1.95)
	Median	-3.76
	Min, Max	-7.87, -1.86
Week 6 (N=14)	Mean (SD)	-3.76 (2.01)
	Median	-3.73
	Min, Max	-6.93, -0.49
Week 8 (N=14)	Mean (SD)	-3.51 (2.01)
	Median	-3.17
	Min, Max	-6.93, -0.20
Week 10 (N=13)	Mean (SD)	-3.50 (2.04)
	Median	-3.54
	Min, Max	-7.11, -0.20
Week 12 (N=14)	Mean (SD)	-3.31 (2.06)
	Median	-2.89
	Min, Max	-6.93, 0.07
Month 6 (N=14)	Mean (SD)	-2.83 (2.25)
	Median	-2.26
	Min, Max	-6.47, 0.46
Month 9 (N=14)	Mean (SD)	-2.48 (2.14)
	Median	-1.86
	Min, Max	-6.47, 0.83
Month 12 (N=13)	Mean (SD)	-2.22 (1.67)
	Median	-2.03
	Min, Max	-5.50, 0.16
Month 15 (N=11)	Mean (SD)	-1.73 (1.68)
	Median	-1.51
	Min, Max	-4.70, 0.22
Month 18 (N=10)	Mean (SD)	-1.29 (1.95)
	Median	-0.79
	Min, Max	-5.64, 0.54
Study Exit (N=14)	Mean (SD)	-1.10 (1.78)
	Median	-1.10
	Min, Max	-4.83, 1.07

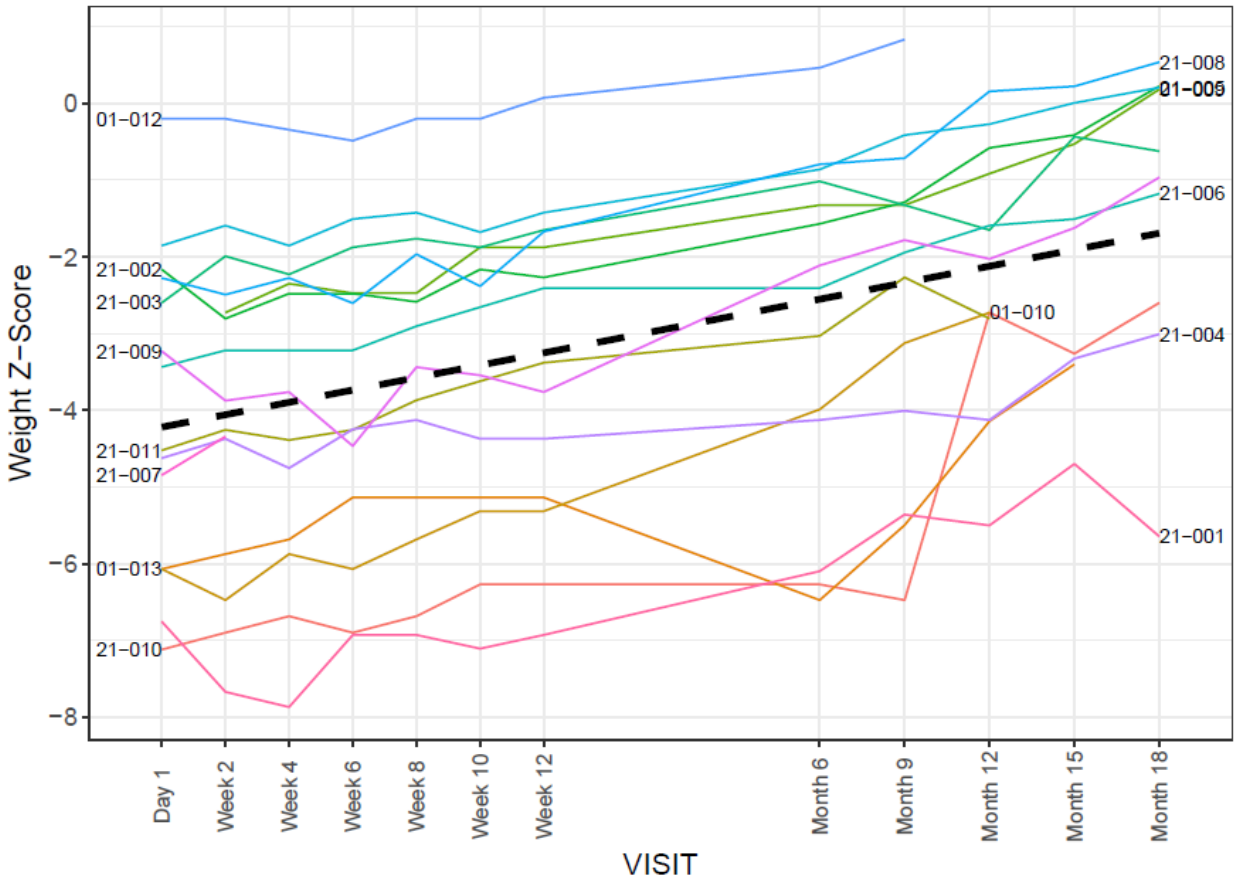
Source: CSR Table 11-10 (p. 85-87)

Figure 5. Standing Weight Using Standardized Norms for Growth Based on Age by Subject



Note: M=male. F=female. BRA=Brazil.
Source: Statistical reviewer's analysis, PD Population

Figure 6. Overall Standing Weight Using Standardized Norms for Growth Based on Age



Note: The dashed line represents a linear regression of weight z-score regressed on visit.
Source: Statistical reviewer's analysis, PD Population

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The CSR reported safety and efficacy results for the subgroups of age < 2 years, age ≥ 2 years, and age < 6 years. Since the focus of this study was on the age < 6 years subgroup, whose primary and secondary efficacy endpoint results were shown in previous sections, and since the study's sample size was small, additional subgroup analyses were not conducted.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Efficacy analyses were pre-specified by the sponsor in the clinical study protocol and determined to be reasonable by the statistical reviewer.

Results for the primary efficacy endpoint indicated that there was a decrease in the mean WBC cystine level during the study's treatment period. However, not all subjects had available WBC

cystine level data at each visit. In addition, some subjects may have had a WBC cystine level < 1 nmol ½ cystine/mg protein at a study visit, but their WBC cystine level did not remain < 1 nmol ½ cystine/mg protein at subsequent visits. Furthermore, since this one study was open-label with a single test drug arm, whether the observed decreasing trend in mean WBC cystine levels and the increasing trend in height and weight during the study's treatment period were clinically meaningful is uncertain. Therefore, one should interpret these findings with caution.

5.2 Conclusions and Recommendations

The statistical reviewer confirmed that there was a decrease in subjects' mean WBC cystine level and an increase in subjects' mean height and weight using standardized norms for growth based on age during the study's treatment period. However, due to concerns of the study being open-label with a single test drug arm, whether the results of the study's efficacy endpoints based on 17 subjects are clinically meaningful is not obvious. We should interpret these findings with caution.

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/s/

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12/01/2017

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