CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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 #:	NDA 203-389
Supplement #:	0000
Drug Name:	PROCYSBI™ (cysteamine bitartrate delayed-release 25 mg and 75 mg capsules; RP103); twice daily orally as a capsule
Indication(s):	Management of Nephropathic Cystinosis in Children and Adults
Applicant:	Raptor Therapeutics, Inc.
Date(s):	Stamp Date: March 30, 2012 PDUFA Goal date: April 30, 2013
Review Priority:	Standard with Major Amendment (13 month review cycle)
Biometrics Division:	Division of Biometrics III
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Keywords: NDA review, Clinical Studies, Active Control/Non-Inferiority

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

There appears to be sufficient evidence to support an efficacy claim for PROCYSBI™ (RP103), and the claims reflected within the applicant's submitted product label are supported by the results shown in this review. The efficacy of RP103 was primarily demonstrated in the single study RP103-03. In this trial, RP103 was demonstrated to be non-inferior to CYSTAGON® with regard to steady-state cysteamine-trough white blood cell (WBC) cystine levels. The study's design was adequate, and the applicant's corresponding analysis plan and results are deemed appropriate to support the proposed indication. A potential statistical issue pertained to justification of the non-inferiority margin. From a statistical perspective it was not feasible to assess constancy and subsequent assay sensitivity when evaluating the non-inferiority margin, as the margin, and the overall design of RP103-03, was primarily based on the results of a seven patient Dohil, Fidler study as described below in Section 3.2.1. The margin was however deemed acceptable by the clinical review team, as was the clinical meaningfulness of the WBC cystine endpoint. Hence, the results from trial RP103-03 are suitable for efficacy claims in the labeling. The sustained efficacy profile shown during the extension study RP103-04 further supports the efficacy of RP103.

2 INTRODUCTION

2.1 Overview

On March 30, 2012, Raptor Therapeutics, Inc. submitted this New Drug Application (NDA) for PROCYSBI™ (Cysteamine Bitartrate delayed-release 25 mg and 75 mg capsules; RP103) pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21, Part 314 of the Code of Federal Regulations. The active pharmaceutical ingredient of RP103 (to be orally administered as a capsule twice daily, BID) is cysteamine bitartrate. Effective on May 17, 2009, RP103 had initiated clinical development under IND 103,694 in patients with Nephropathic Cystinosis, and has been developed specifically to establish safety and efficacy in this patient population. The proposed indication for RP103 is the management of nephropathic cystinosis in children and adults. Raptor Therapeutics obtained *Orphan Designation* from the Office or Orphan Products Development (OOPD) on October 24, 2006.

Cystinosis is an autosomal recessive inborn error of metabolism, in which the transport of cystine out of lysosomes is reduced or absent. Nephropathic cystinosis is a rare inherited condition, which causes the buildup of a protein building block, called cystine, in every cell of the body. The condition is fatal in early childhood, if left untreated, and is thought to affect fewer than 500 patients in the United States in total. The accumulation of cystine and the formation of crystals may damage various organs. The kidneys are usually the first organs to present clinical signs by the buildup of cystine. Cytinosis causes the body to lose too much sugar (glucose), proteins, and electrolytes, and quickly leads to kidney failure which ultimately requires a transplant. Cytinosis also leads to low body growth, weak bones, diabetes, thyroid and neurological complications, and muscle atrophy. One of the main causes of death, independent of age, is pneumonia and respiratory distress due to swallowing impairment.

Currently, there are FDA-approved treatment options for patients with nephropathic cystinosis, e.g. CYSTAGON® (NDA 20-392), which is the reference drug and the basis for this 505(b)(2) application. CYSTAGON also has cysteamine bitartrate as its active ingredient with an immediate release formulation, and is administered in 50 mg and 150 mg capsules. RP103 is a delayed-release version of CYSTAGON and not a New Molecular Entity (NME). Since its approval in 1994, CYSTAGON is considered to be the standard therapy for treating patients with nephropathic cystinosis and is the only therapy currently available to treat nephropathic cystinosis in the US. If taken as indicated, it can significantly slow the progression of the disease. Unfortunately, poor patient compliance with CYSTAGON therapy is widely acknowledged in the cystinosis medical and patient community. Poor or sporadic patient compliance has been reported to result in continued organ deterioration. Most frequently reported reasons for poor compliance include the requirement for a strict every six-hour around the clock dosing schedule, especially a midnight to 1:00 AM dose, associated dose dependant nausea, and the taste and smell. The correlation between length of exposure to cysteamine bitartrate and evidence of beneficial outcomes has led to frustration within the cystinosis community, due to the widespread challenges in remaining compliant on the immediate-release formulation. Consequently, nephropathic cystinosis remains as a rare, serious and life threatening condition without a fully met medical need.

RP103 is an enteric-coated microbead formulation that permits a reduction of dose frequency and potentially a lower overall daily dose of the drug and may provide other substantial advantages over CYSTAGON. As previously stated, RP103 is a more palatable, delayed-release form of cysteamine bitartrate. Additionally, RP103 may avoid some of the unwanted side effects of the compound and extend the duration of effective treatment to a Q12H (every 12 hours) dosing regimen, thereby helping to improve compliance over the current Q6H (every 6 hours) dosing required for CYSTAGON. Moreover, the enteric-coated microbeads of RP103 can be sprinkled directly onto food which is easier to dose infants and children too young to take intact capsules. As cystinosis is usually diagnosed by age one, adequate treatment during early years is critical to support organ development.

The clinical efficacy and safety of RP103 has been primarily evaluated in one trial: a phase 3, multicenter, randomized, active controlled, cross-over, non-inferiority study (RP103-03), which serves as the single adequate and well controlled study in this clinical development program. Table 1 below presents information on this pivotal clinical trial contained in the submission.

Table 1
Summary Information for Relevant Clinical Trials

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Patients	Patient Diagnosis	Duration of Treatment
Efficacy and Safety; Phase 3	RP103-03	Demonstrate non-inferiority of RP103 vs. CYSTAGON in reducing WBC cystine	Multicenter, randomized, open-label, active controlled, cross-over, non-inferiority	Treatment Arm A: RP103 Q12H followed by CYSTAGON Q6H, Treatment Arm B: CYSTAGON Q6H followed by RP103 Q12H; BID; Oral in 25 mg and 75 mg capsules;	Total: 43	Patients (mostly children) with nephropathic cystinosis	8 weeks (3 weeks treatment with RP103 and 5 weeks treatment with CYSTAGON due to 2 week active Run-In period)

Source: Reviewer's Table.

2.2 Data Sources

This NDA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). Its content, including the electronic data sets and labeling information, is located in the electronic document room (EDR) at this path location: \\Cdsesub1\evsprod\NDA203389. Sequences 0000, 0006, 0016, 0024, and 0026 contain all the contents relevant for this review.

For study RP103-03, the applicant's clinical study report (CSR), clinical datasets and analysis datasets were reviewed. The clinical datasets were compliant to the CDISC/SDTM v.3.1.2 implementation guide standard, and the analysis datasets were compliant to the CDISC/ADaM v.1.0 implementation guide standard. Adequate data definition files, in Define.XML and Define.PDF formats, and software code, in .SAS format, were also submitted for the study.

3 STATISTICAL EVALUATION

The statistical evaluation is for pivotal trial RP103-03 only.

3.1 Data and Analysis Quality

This study utilized Case Report Forms (CRF), and the submitted data quality and integrity appeared to be adequate upon the initial submission. However, later in the review cycle, Raptor Therapeutics, Inc. notified Division of Gastroenterology and Inborn Errors Products (DGIEP)

that the central laboratory utilized in the study, [redacted] (b) (4) made measurement errors when assessing WBC cystine levels. As indicated below in Section 3.2.1, the level of WBC cystine was utilized in the primary endpoint for this study. This initial error resulted in reported WBC cystine levels being greater than their true values. The correction of these concentration levels resulted in a numerical reduction of approximately 25% of the initially reported values. The applicant consequently submitted an updated CSR, along with updated clinical and analysis efficacy lab datasets, in order to reflect the corrected results. As presented in Section 3.2.4 below, it was shown that the overall study conclusions were not affected by this central laboratory measurement error.

It was possible to reproduce the primary analysis dataset (along with the numerical results presented within the updated CSR), specifically the primary endpoint values, from the original data source. It was possible to verify the randomized treatment assignments, and the applicant submitted documentation of data quality control/assurance procedures within Section 9.6 of their ICH E3 compliant CSR.

The applicant's statistical analysis plan (SAP) was finalized on December 6, 2010. The SAP was amended once. The original SAP was signed off/issued on October 21, 2010. The applicant decided to make minor changes pertaining to data presentation and did so on December 6, 2010 (the finalized SAP issued). These changes were made independent of the study itself. No changes to the analyses themselves were made. The SAP was submitted, and all relevant analysis decisions were made before trial completion (June 3, 2011) and the planned interim analysis (January 17, 2011). Database hard-lock was on June 17, 2011.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Phase 3 efficacy and safety study RP103-03 is an adequate and well-controlled study that is the basis for efficacy claims in the labeling. Due to the orphan status of nephropathic cystinosis, there was only one small clinical safety and efficacy study conducted by Raptor Therapeutics, Inc. prior to RP103-03. That was a Phase 1 study, RP103-01, which had nine patients in total, and was a single-dose, open-label and non-randomized clinical trial. In addition to study RP103-01, the literature studies, prominently the Dohil, Fidler et al. 2010 study[1], were used to help the design of this pivotal clinical trial. The applicant submitted this study under IND 103,694 as a Special Protocol Assessment (SPA) on March 3, 2010. DGIEP issued a no-agreement letter to the applicant on April 16, 2010, which motivated the applicant to resubmit the SPA on May 11, 2010. Raptor eventually withdrew the SPA on June 28, 2010 in order to proceed with the trial after DGIEP denied the resubmission of the SPA on May 12, 2010.

RP103-03 began screening patients on June 23, 2010, and it was completed on June 3, 2011. The original protocol for this study was issued on November 21, 2009. The final version of this protocol, after a series of amendments through separate communications with DGIEP, was

[1] Dohil, R., M. Fidler, et al. (2010). "Twice-Daily Cysteamine Bitartrate Therapy for Children with Cystinosis." J Pediatr.

issued on October 22, 2010. These amendments included administrative changes along with incorporation of DGIEP input, and had minimal impact on trial conduct, e.g., study treatment, duration or procedures.

This was a nine-week, multicenter (with a total of eight clinical sites; three in the USA and five in Europe), out-patient, randomized, open-label, active controlled, cross-over, non-inferiority trial, whose primary objective was to assess the non-inferiority of RP103 to CYSTAGON by evaluating WBC cystine concentration levels in pediatric patients with nephropathic cystinosis. To be enrolled into the study, patients must have been on a stable dose of CYSTAGON considered sufficient to maintain their WBC cystine level at least 2.0 nmol/½ cystine/mg protein. This stable dose, determined during a one week screening period (Week 1), was unique for each patient.

The study consisted of two treatment periods: Period 1 (Weeks 4 through 6; ±3 days) and Period 2 (Weeks 7 through 9; ±3 days). Prior to treatment, eligible patients underwent a two-week Run-in Period (Weeks 2 through 3) of CYSTAGON administered every six hours. Available safety data and WBC cystine levels collected during this Run-in period were reviewed to confirm study eligibility. On Week 3, Day 7, patients (who had their eligibility confirmed) were randomized (in an open-labeled fashion and on a 1:1 ratio, in accordance with a computer-generated central randomization schedule) to one of the two treatment sequences: Treatment Arm A – three weeks (Period 1: Weeks 4 through 6; ±3 days) treatment with RP103 every 12 hours followed by crossover to three weeks (Period 2: Weeks 7 through 9; ±3 days) of CYSTAGON every six hours; or Treatment Arm B – three weeks (±3 days) treatment with CYSTAGON every six hours followed by crossover to three weeks (±3 days) of RP103 every 12 hours. Patients were stratified based on their WBC cystine level during the Run-in Period: Group L with at most 1.0 nmol/½ cystine/mg protein and Group H with more than 1.0 and less than or equal to 2.0 nmol/½ cystine/mg protein. It should be noted that RP103 was administered in 25 mg and 75 mg capsules while CYSTAGON was administered in 50 mg and 150 mg capsules. These treatment periods are presented in Table 2 below.

Table 2
Treatment Periods in RP103-03

Treatment Arm	Period 1 (Weeks 4 through 6; ±3 days)	Period 2 (Weeks 7 through 9; ±3 days)
A	RP103 Q12H	CYSTAGON Q6H
B	CYSTAGON Q6H	RP103 Q12H

Source: Reviewer's Table.
Note: Week 1 pertains to study screening while Weeks 2 and 3 are designated for active run-in with CYSTAGON.

Patients receiving RP103 were asked not to take any proton pump inhibitors (PPIs) or gastric acid reducing medications from 12 hours prior to their first RP103 dose to study completion. Note that the treatment crossover was immediate with no washout period instituted. In addition, the starting daily dose of RP103 for Periods 1 and 2 was 70% – 80% of the total daily dose of CYSTAGON administered during the Run-in Period (and due to the uniqueness of each patient's total daily CYSTAGON dose, each patient's total daily RP103 dose was also unique). A potentially optional increase of 25% of the actual dose of RP103 could be made that corresponds to 92% to 100% of the Run-in CYSTAGON dose. This optional increase depended on WBC

cystine levels and safety data while subjects were taking RP103 either during Week 5 (corresponding to Period 1) or Week 8 (corresponding to Period 2).

In the RP103-03 CSR, Raptor stated the following reasons why blinding was not feasible in this study:

1. The dosage forms for CYSTAGON are twice the strength of RP103. Moreover, CYSTAGON is administered four times daily and RP103 is administered twice daily. The planned dose for RP103 is not a simple multiple of the CYSTAGON dose. The planned total daily RP103 starting dose is 70% to 80% of the total daily CYSTAGON dose. With allowed dose adjustments, the administration schedule is even more complicated. Therefore the risk of over-exposure to study drug is considerable since a mixture of placebo capsules and CYSTAGON capsules would need to be taken together in order to administer the same number of capsules Q6H as Q12H with RP103 plus placebo, i.e., there is increased risk if the subject accidently takes CYSTAGON + CYSTAGON instead of CYSTAGON + placebo thereby overdosing themselves with CYSTAGON. In addition, it would be very difficult for the patient to adapt and comply with the dose changes that may occur at Week 5 and 8, and still maintain the blinding of the study. The problem is further compounded since every patient's cysteamine dose is variable and is determined not by body weight but by their final level of WBC cystine; this is why blinding would not be a feasible solution as well.
2. The use of an over-encapsulation was not feasible because the largest dosage form for both CYSTAGON and RP103 is a size 0 capsule and if over-encapsulated, would be substantially larger. Most patients who will qualify for study participation are young, pre-transplant subjects who have swallowing difficulties and are simply too small to be able to orally ingest capsules much larger than a size 0 capsule, thus obviating the use of an over-encapsulating approach to blind the study.
3. To facilitate blinding, regardless of the issues identified above, Raptor considered presenting RP103 in two different vials, i.e., vial A and vial B, where vial A would contain RP103 to be taken at 6:00 am and 6:00 pm, and vial B would contain a placebo to be taken at noon and midnight. However, alternating placebo and cysteamine would unblind the study due to the difference of the smell of the capsules. In addition, post-dosing bad breath is associated with each dose of cysteamine bitartrate; a factor that would immediately result in breaking the blind.

In addition to no blinding, a washout was not instituted in the crossover between Periods 1 and 2. A washout period was not deemed necessary by the applicant due to the short half life and dosing regimen of each treatment: RP103 every 12 hours with an average half-life of 5.85 hours (with a standard deviation of 2.89 hours) per dose; CYSTAGON every six hours with an average half-life of 1.90 hours (with a standard deviation of 0.58 hours) per dose.

It should be noted that all patients who were randomized into this study were later given the opportunity to immediately roll over into a 24-month, multicenter, open-label, un-controlled extension study (trial RP103-04) which assesses the long term efficacy and safety of RP103.

The primary objective of this study was to demonstrate that at steady-state, patients receiving an every six hour treatment regimen of CYSTAGON can maintain a comparable depletion of WBC

cystine levels after receiving an every 12 hour treatment regimen of RP103. The secondary objectives of the study were to assess the safety and tolerability of RP103, and to assess the steady-state pharmacokinetics (PK) and pharmacodynamics (PD) of RP103 compared to CYSTAGON.

The primary study objective would be met through a non-inferiority comparison, using WBC cystine levels at steady-state, between RP103 and CYSTAGON. PD sampling for WBC cystine levels was conducted at specified time points throughout this nine-week study as indicated by the schedule of assessments. Depending on the location of the clinical site, the samples were processed by one of the two central laboratories; one in the USA and the other in Europe. The sampling results utilized for the primary objective were obtained during the last three days of each treatment period, when steady-state was expected, i.e. Days 5, 6, and 7 of Week 6 (for Period 1) and Days 5, 6, and 7 of Week 9 (for Period 2).

The following primary endpoint was pre-specified by the applicant:

Primary Endpoint: The primary endpoint was the steady-state cysteamine-trough WBC cystine levels on Days 5, 6 and 7 of Week 6 (Period 1) and on Days 5, 6 and 7 of Week 9 (Period 2). A non-inferiority hypothesis test was utilized to assess whether the WBC cystine levels between RP103 and CYSTAGON were comparable. As previously stated, the repeated measurements taken during the last three days of each treatment period are when the drugs were expected to be at steady-state. In addition, these timepoints correspond to the trough of cysteamine concentration. It should also be noted that lower WBC cystine levels are thought to be clinically meaningful, i.e., an improvement in disease state, because they are thought to be associated with less actual cellular cystine levels (which are difficult to directly measure). White blood cell (WBC) cystine levels have been used as a proxy/surrogate to the actual cystine levels within cells themselves. Moreover, as discussed previously in Section 2.1 above, lower cellular cystine levels are salubrious; higher cellular cystine levels are deleterious and associated with eventual organ damage.

There were no formal secondary endpoints pre-specified by the applicant. With respect to the primary endpoint, a non-inferiority margin of 0.30 nmol/½ cystine/mg protein was chosen given that the goal of therapy is to maintain WBC cystine level depletion below 1.0 nmol/½ cystine/mg protein and that WBC cystine level depletion with CYSTAGON is, on average, 0.70 nmol/½ cystine/mg protein (Dohil, Fidler et al. 2010). Hence the tested hypotheses (which incorporate this non-inferiority margin), with μ_R and μ_C signifying mean WBC cystine levels when being treated with RP103 and CYSTAGON, respectively, were defined as follows:

$$H_0: \ \mu_R - \mu_C \geq 0.3 \text{ vs. } H_1: \ \mu_R - \mu_C < 0.3$$

The initial sample size calculation was based on a University of California San Diego (UCSD) study (Dohil, Fidler et al. 2010) of weekly steady-state serial measurements of WBC cystine levels from seven patients treated with CYSTAGON followed by treatment with an enteric-coated cysteamine bitartrate (i.e. EC-CYSTAGON). Under this study design each patient could contribute eight observations for a total of 56 observations. A repeated measures analysis of variance within the linear mixed effects model framework was used to fit these data and estimate

the intra-subject mean of WBC cystine and the corresponding variance. The covariance matrix used in this model had a compound-symmetry structure. The initial estimate of sample size for RP103-03 was based on the results of this UCSD study. The following, including the previously presented null and alternative hypotheses, were the assumptions for the sample size calculation:

- Estimated WBC cystine level on CYSTAGON, $\mu_C = 0.70$ (as previously stated)
- Expected WBC cystine level on RP103, $\mu_R = 0.70$
- Intra-subject variance, $\sigma^2_e = 0.137$
- One-sided $\alpha = 0.025$

Based on the above assumptions, 16 subjects would provide 90% power to reject the null hypothesis. This calculation was made using the normal approximation formula:

(b) (4)

(b) (4)

The applicant, however, was uncertain regarding the initially estimated intra-subject variance, σ^2_e. As one can deduce from the previously presented sample size formula, if the true variance was larger than 0.137, the trial would have been underpowered. Consequently the applicant utilized a sample size re-estimation procedure with one interim analysis for the sole purpose of a re-estimation of the overall sample size through an open-label re-estimation of the intra-subject variance, σ^2_e. The amount of one-sided α spent by the sponsor on this interim analysis was pre-specified to be 0.00396. Hence, the one-sided α for providing 90% power to reject the null hypothesis in the final analysis became (b) (4) for controlling the overall study Type I error rate.

This two-stage sample size re-estimation procedure was as follows:

1. Enroll 20 subjects and estimate σ^2_e. Substitute this new estimate into the sample size formula above, while also incorporating into the calculation the new one-sided α = (b) (4), and re-compute the sample size. Subjects who drop out of treatment following randomization will also be included in the sample size re-estimation. If the sample size so computed is less than or equal to 30, continue enrollment until 30 subjects are enrolled. Otherwise proceed to Stage 2.
2. Continue enrolling subjects until a total of n subjects (based on the sample size formula above with the revised estimate of σ^2_e and the new value for α) have been enrolled, subject to an upper limit of $n \leq 50$. Terminate the trial and perform the final analysis.

The planned interim analysis was conducted on January 17, 2011; however, the data was properly analyzed on February 11, 2011. The new estimate for (b) (4) and with (b) (4) (b) (4), hence, the final sample size calculation was (b) (4) As discussed below in Sections 3.2.3 and 3.2.4, due to the unexpected availability of patients, the total number of patients actually randomized into the study was 43.

Statistical non-inferiority would be demonstrated if the one-sided null hypothesis presented above, conducted at $\alpha = 0.02104$, is rejected, i.e. if the one-sided p-value of the test statistic associated with the difference in Least Squares (LS) Means (generated from a linear mixed effects model; see Section 3.2.2.2 below) between the two treatment groups is < 0.02104. Equivalently, if the upper bound of the one-sided 97.9% Confidence Interval (CI), or two-sided 95.8% CI, is strictly less than 0.30, then non-inferiority could be demonstrated. In that case, it can be concluded that RP103 is non-inferior to CYSTAGON.

Formal statistical hypothesis testing was performed on the primary endpoint. Hence, there was no multiplicity adjustment strategy instituted for this trial in order to control the overall study Type I error rate.

Overall, the design of study RP103-03 was deemed adequate. The primary endpoint and non-inferiority margin were adjudicated by the review team as clinically meaningful, and the estimated sample size was validated and confirmed as appropriate. The open-label nature of the study was acceptable per the explanation by Raptor above, and, due to the objective laboratory measuring of the endpoint itself, would not be expected to introduce bias. The justification of not instituting a washout period during the crossover was also deemed acceptable per the explanation given by the applicant. It is shown in Section 3.2.4 below that, as expected, there was no treatment-by-period interaction in this study. It was not feasible to assess constancy and subsequent assay sensitivity when evaluating the proposed non-inferiority margin of 0.30 from a statistical perspective. This was due to the fact that this margin, and the overall design of RP103-03, was primarily informed by the results of the seven patient Dohil, Fidler et al. 2010 study as previously described.

3.2.2 Statistical Methodologies

3.2.2.1 Analysis Sets

The primary analysis set, i.e. the analysis set used for all primary analyses, was the Per-Protocol (PP) analysis set. This analysis set includes all randomized patients with at least one WBC cystine level on Days 5, 6, or 7 of Week 6 (Period 1) and at least one WBC cystine level on Days 5, 6, or 7 of Week 9 (Period 2), while excluding those patients who meet at least one of the following conditions corresponding to measurements when being treated with CYSTAGON:

- Average WBC Cystine levels > 2 during the Run-in (Day 3, 4, 5)
- Average WBC Cystine levels > 2 during Period 1 (Week 4) {for patients receiving CYSTAGON during Period 1}
- Average WBC Cystine levels > 2 during Period 1 (Week 6) {for patients receiving CYSTAGON during Period 1}
- Average WBC Cystine levels > 2 during Period 2 (Week 7) {for patients receiving CYSTAGON during Period 2}
- Average WBC Cystine levels > 2 during Period 2 (Week 9) {for patients receiving CYSTAGON during Period 2}

In this analysis set, patients were included in the treatment group, based on period, within the treatment sequence that they actually received.

All analyses were confirmed by utilizing the "efficacy analysis set" proposed by the applicant, which includes all randomized patients with at least one WBC cystine level on Days 5, 6, or 7 of Week 6 (Period 1) and at least one WBC cystine level on Days 5, 6, or 7 of Week 9 (Period 2). This analysis set is the PP analysis set without the additional exclusion conditions listed above. In this analysis set, patients were included in the treatment group, based on period, within the treatment sequence that they were randomized to receive regardless of actual treatment sequence received. This analysis set will be referred to as Modified Intent-to-Treat (mITT) throughout the remainder of this review.

All analyses were repeated, for sensitivity analysis purposes, utilizing an All-Randomized analysis set which includes all patients who were randomized into the study. In this analysis set, patients were included in the treatment group, based on period, within the treatment sequence that they were randomized to receive regardless of actual treatment sequence received.

Overall, the utilization of the applicant defined analysis sets is acceptable. Specifically, per ICH E9, the use of the PP analysis set as the primary analysis set may be preferable as this is a non-inferiority study; however, all analysis sets (specifically both the PP and All-Randomized analysis sets) are utilized for the primary analysis in order to comply with FDA's Guidance for Industry: Non-Inferiority Clinical Trials[2].

3.2.2.2 Primary Endpoint Analysis

A repeated measures analysis of variance within the linear mixed effects model framework was used as the primary analysis method. The response vector consisted of repeated measures of WBC Cystine levels during Days 5, 6, and 7 of Week 6 (Period 1) and Days 5, 6, and 7 of Week 9 (Period 2). Treatment Sequence, Period within Treatment Sequence, Treatment and Day were utilized as fixed effects. Since similarly spaced time points are expected to have similar covariances, as was the case with this WBC data, the covariance matrix in this model had a *Toeplitz* structure in order to model the covariance across these time points. For sensitivity analysis purposes, different covariance matrix structures were explored, e.g., first order auto-regressive, compound-symmetry, and unstructured. The significance level for the hypothesis test, described in Section 3.2.1 above, and its corresponding two-sided 95.8% CI (as opposed to the equivalent one-sided 97.9% CI) were the inferential statistics chosen for the presentation. The treatment-by-period interaction was also assessed.

3.2.2.3 Handling of Dropouts/Missing Data

The primary approach for handling missing data utilized a strategy which imputed no-change-from-baseline/Run-in WBC cystine levels for missing Days 5, 6, and 7 of Week 6 (Period 1) or Days 5, 6, and 7 of Week 9 (Period 2). As discussed in Section 3.2.3 and 3.2.4 below, there were only two patients who dropped out of this study, and sensitivity analyses subsequently showed that this did not impact the study results.

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition information for all randomized patients is displayed in Table 3 below, which is presented by randomized treatment sequence. It should be noted that there were no patients whose actual treatment sequence differed from their randomized treatment sequence. The notation X → Y signifies that treatment X is followed by treatment Y.

Table 3
Disposition – Study RP103-03
(All Randomized)

	RP103-03 → CYSTAGON (N = 22)	CYSTAGON → RP103 (N = 21)	Total (N = 43)
Randomized	22 (100%)	21 (100%)	43 (100%)
Modified Intent-to-Treat (mITT) [1]	20 (90.9%)	21 (100%)	41 (95.3%)
Per-Protocol (PP) [2]	19 (86.4%)	20 (95.2%)	39 (90.7%)
Completed Study	20 (90.9%)	21 (100%)	41 (95.3%)
Completed 1st Period of Treatment	20 (90.9%)	21 (100%)	41 (95.3%)
Completed 2nd Period of Treatment	20 (90.9%)	21 (100%)	41 (95.3%)
Discontinued Study Early	2 (9.1%)	0	2 (4.7%)
Adverse Event	1 (4.5%)	0	1 (2.3%)
Death	0	0	0
Lack of Efficacy	0	0	0
Lost to Follow-up	0	0	0
Physician Decision	0	0	0
Protocol Violation	0	0	0
Study Terminated by Sponsor	0	0	0
Withdrawal of Consent	0	0	0
Continued Non-Compliance with Diaries	0	0	0
Other	1 (4.5%)	0	1 (2.3%)

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment sequence or overall.
[1]: Patients 01-002 (Adverse Event) and 01-003 (Other) withdrew from the trial prior to the completion of Treatment Period 1.
[2]: Patients 02-014 and 03-009 were dropped from the mITT analysis set due to having WBC cystine levels >2.0 nmol/½ cystine/mg protein.

The demographics and baseline characteristics for all randomized patients is presented in Table 4 below. Table 4 is also presented by randomized treatment sequence.

Table 4
Demographic and Baseline Characteristics – Study RP103-03
(All Randomized)

	RP103-03 → CYSTAGON (N = 22)	CYSTAGON → RP103 (N = 21)	Total (N = 43)
Age (years)			
n	22	21	43
Mean (SD)	11.3 (4.77)	12.2 (3.53)	11.7 (4.19)
Median	10.5	13.0	11.0
Min, Max	6, 26	6, 18	6, 26
Age Group – n (%)			
≥ 18 (Adult)	2 (9.1%)	1 (4.8%)	3 (7.0%)
13 – 17 (Adolescent)	3 (13.6%)	10 (47.6%)	13 (30.2%)
2 – 12 (Child)	17 (77.3%)	10 (47.6%)	27 (62.8%)
Geographic Region			
USA	12 (54.5%)	14 (66.7%)	26 (60.5%)
Europe	10 (45.5%)	7 (33.3%)	17 (39.5%)
Gender – n (%)			
Female	8 (36.4%)	11 (52.4%)	19 (44.2%)
Male	14 (63.6%)	10 (47.6%)	24 (55.8%)
Race – n (%)			
White/Caucasian	22 (100%)	20 (95.2%)	42 (97.7%)
Other	0	1 (4.8%)	1 (2.3%)
Run-in Average WBC Cystine Level (nmol/½ cystine/mg protein)			
n	22	21	43
Mean (SD)	0.477 (0.2153)	0.502 (0.2915)	0.489 (0.2526)
Median	0.488	0.488	0.488
Min, Max	0.14, 1.01	0.09, 1.22	0.09, 1.22
Run-in Average WBC Cystine Level Group (nmol/½ cystine/mg protein)			
≤ 1.0	21 (95.5%)	20 (95.2%)	41 (95.3%)
> 1.0 – ≤ 2.0	1 (4.5%)	1 (4.8%)	2 (4.7%)
Prescribed CYSTAGON Daily Dose (mg)			
n	22	21	43
Mean (SD)	1713.6 (505.49)	1842.9 (612.63)	1776.7 (557.45)
Median	1600.0	1800.0	1800.0
Min, Max	1000, 3000	900, 3000	900, 3000
Prescribed RP103 Daily Dose (mg)			
n	22	21	43
Mean (SD)	1272.7 (368.31)	1397.6 (361.41)	1333.7 (366.08)
Median	1175.0	1250.0	1250.0
Min, Max	850, 2400	850, 2100	850, 2400

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment sequence or overall.

There is no significant imbalance between the treatment sequences regarding the presented demographic and baseline characteristics. It should be noted that this patient sample consisted primarily of Caucasians who were between 6 and 17 years of age (93%), inclusively.

3.2.4 Results and Conclusions

The results displayed in this section correspond exclusively to the primary endpoint as defined in Section 3.2.1 above. As stated previously, there were no secondary efficacy endpoints pre-specified for this study and hence no corresponding results to report.

Table 5
Analysis of WBC Cystine Levels by Treatment Group – Study RP103-03 (PP)

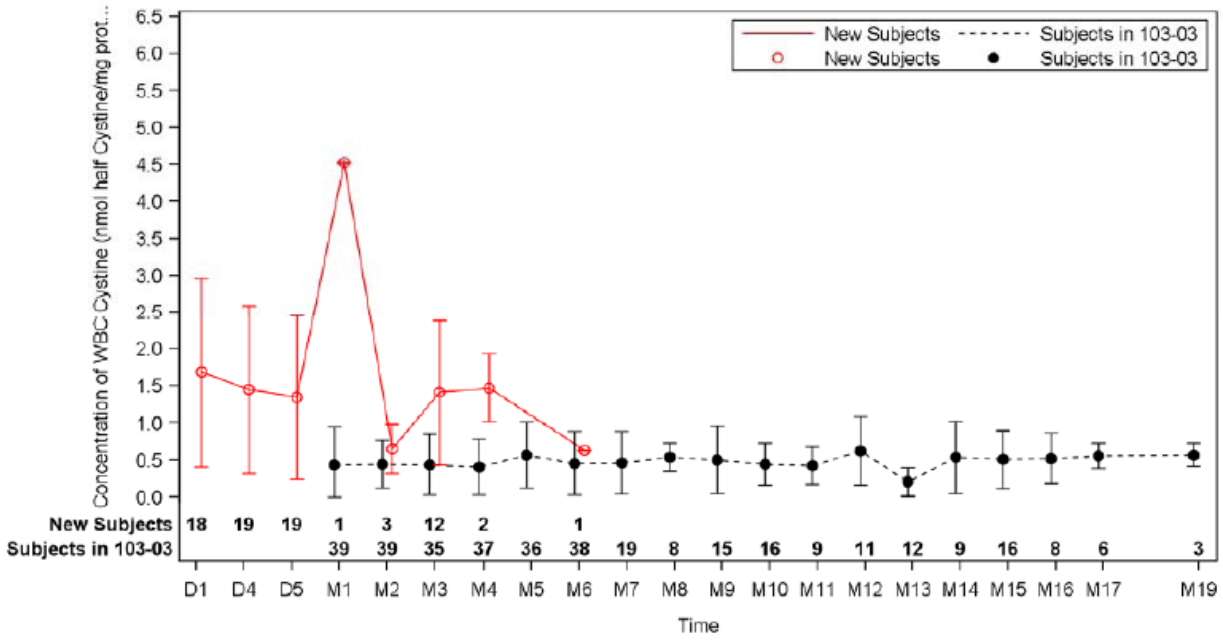
	Study Treatment		Difference Between RP103 and CYSTAGON (i.e. RP103 – CYSTAGON)
	RP103 (N = 39)	CYSTAGON (N=39)	
LS Means (SE) [1]	0.5152 (0.05555)	0.4367 (0.05555)	
Difference in LS Means (SE)			0.0785 (0.0323)
Two-sided 95.8% CI of Difference in LS Means			(0.0107, 0.1464)

Source: Reviewer's Table.
Note: WBC Cystine Levels are measure in nmol/½ cystine/mg protein.
[1]: Obtained by a repeated measures analysis of variance within the linear mixed effects model framework with Treatment Sequence, Period within Treatment Sequence, Treatment and Day utilized as fixed effects. The covariance matrix in this model had a Toeplitz structure.

Overall, it can be seen that the upper two-sided 95.8% CI limit of 0.1464 is less than 0.30 and hence non-inferiority can be concluded. These analyses were all repeated utilizing the mITT and All-Randomized analysis sets with no changes to the conclusions. In fact, the results using the PP analysis set were the most conservative, i.e., the upper limit of the two-sided 95.8% CI was less than 0.1464 when using the mITT (upper limit equal to 0.0635) and All-Randomized (upper limit equal to 0.0609) analysis sets. In addition, for sensitivity analysis purposes, different covariance matrix structures were explored, including first order auto-regressive, compound-symmetry, and unstructured, with no changes to the conclusions. From the 43 patients who were originally randomized, there were only two dropouts; sensitivity analysis subsequently showed that these two dropouts did not impact the study results. It was also determined that there was no treatment-by-period interaction. There were too many sites (eight in total) relative to the total number of patients randomized (i.e., 43), however it is important to note that no single site influenced or drove the overall study results. There were two outliers (patients 02-014 and 03-009). These two patients were not included in the PP analysis but were within the mITT analysis set, and, as previously stated, the study results and conclusions were consistent between these two analysis sets. Finally, the overall study conclusions were not affected by the previously described central laboratory measurement error as the originally reported two-sided 95.8% CI of the Difference in LS Means was (-0.0065, 0.1683).

As stated previously in section 3.2.1, all patients participating in study RP103-03 were eligible to roll over into the long term efficacy and safety trial RP103-04. In the end, out of the 43 patients randomized into the RP103-03 study, 40 participated in RP103-04, and Figure 1 below displays the long term WBC cystine levels across this entire 24 month open-label study (which is currently ongoing) for these 40 patients. In addition, WBC cystine levels for 20 patients newly recruited into RP103-04, who did not participate in RP103-03, are also presented.

Figure 1
Mean (± SD) WBC Cystine Levels by Quarterly Visit – Studies RP103-03/RP103-04 (RP103-03 Randomized patients rolling over into RP103-04; New RP103-04 patients who did not participate in RP103-03)



Source: 120 Day Safety Update (Sequence 0026 on 30Jan2013) - Figure 3 on pg. 62.
Note: WBC Cystine Levels are measure in nmol/½ cystine/mg protein. The minimum of the mean minus SD is set to 0 nmol/½ cystine/mg protein. "D" represents "Day" and "M" represents "Month".

As can be seen from Figure 1, patients who enrolled in the RP103-04 study after completing the RP103-03 study (n=40; solid back circles) have low, well-maintained mean WBC cystine levels at study entry and have continued to have low, well-maintained mean WBC levels up through Month 19 of the RP103-04 study. In contrast, for the newly recruited patients (who were transplanted and were ≤ 6 years old; n=20; open red circles) it was not requested, per protocol, to be previously well controlled (i.e., WBC cystine level at most 1 nmol/½ cystine/mg protein) under CYSTAGON prior to trial participation. Consequently, the investigators were, at the time of the NDA submission, adjusting the dose of RP103 for these patients, as it is standard of care with cysteamine treatment, after starting at a RP103 daily dose of 70% of their previous daily dose of CYSTAGON. It is anticipated, based on the trend already seen with the RP103-03 patients, that when more of the newly recruited patients have completed longer durations of treatment, consistent control of WBC cystine levels will be achieved.

It was determined that RP103 was non-inferior to CYSTAGON based on the primary analysis of WBC cystine levels. Hence regarding contribution to the overall level of evidence, the results within trial RP103-03 are viewed positively as the formal basis for efficacy claims in the labeling. A consideration that needs to be made pertaining to how the RP103 dose is to be labeled is that a given patient's dose, as described in Section 3.2.1, was a function of that patient's unique and stable CYSTAGON dose. It should be noted that 24 patients had their RP103 dose adjusted during the RP103-03 trial; the adjusted doses ranged between 84% and 120% of the CYSTAGON Run-in dose.

3.3 Evaluation of Safety

As communicated in the clinical review, the overall safety profile of RP103 appears to be similar to the reference product CYSTAGON, although a higher incidence of gastrointestinal adverse events were observed in trial RP103-03 when comparing RP103 with CYSTAGON. During the entire RP103 development program, there were no deaths and two treatment-related serious adverse events. Non-serious adverse events occurring in more than 5% of patients were vomiting, nausea, abdominal pain, dizziness, and headaches. See Section 7 of the clinical review for full details regarding the safety profile of RP103.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

In study RP103-03, the majority of randomized patients (i.e. 93%) were Caucasians who were between 6 and 17 years of age, inclusively. Hence, race and age specific subgroup analyses would not be informative. Due to this lack of representation, extrapolation of these study results to patients who are not Caucasian or not between, and including, 6 and 17 years of age should be made with caution.

Efficacy was assessed by gender, and it was found that the results were consistent across the female and male subgroups. These results are presented in Table 6 below.

Table 6
Gender Subgroup Analysis of WBC Cystine Levels by Treatment Group – Study RP103-03 (PP)

	Study Treatment		Difference Between RP103 and CYSTAGON (i.e. RP103 – CYSTAGON)
	RP103 (N = 39)	CYSTAGON (N=39)	
Female			
n	16	16	
LS Means (SE) [1]	0.4627 (0.06443)	0.4171 (0.06468)	
Difference in LS Means (SE)			0.0456 (0.057)
Two-sided 95.8% CI of Difference in LS Means			(-0.081, 0.1722)
Male			
n	23	23	
LS Means (SE) [1]	0.5813 (0.08390)	0.4571 (0.08382)	
Difference in LS Means (SE)			0.1242 (0.0376)
Two-sided 95.8% CI of Difference in LS Means			(0.0430, 0.2053)

Source: Reviewer's Table.
Note: WBC Cystine Levels are measure in nmol/½ cystine/mg protein.
[1]: Obtained by a repeated measures analysis of variance within the linear mixed effects model framework with Treatment Sequence, Period within Treatment Sequence, Treatment and Day utilized as fixed effects. The covariance matrix in this model had a Toeplitz structure.

Efficacy was also assessed by geographic region, and it was found that the results were consistent across the USA and Europe subgroups. These results are presented in Table 7 below.

Table 7
Geographic Region Subgroup Analysis of WBC Cystine Levels by Treatment Group – Study RP103-03
(PP)

	Study Treatment		Difference Between RP103 and CYSTAGON (i.e. RP103 – CYSTAGON)
	RP103 (N = 39)	CYSTAGON (N=39)	
USA			
n	22	22	
LS Means (SE) [1]	0.6112 (0.08738)	0.5205 (0.08709)	
Difference in LS Means (SE)			0.0907 (0.0473)
Two-sided 95.8% CI of Difference in LS Means			(-0.0118, 0.1932)
Europe			
n	17	17	
LS Means (SE) [1]	0.3777 (0.05642)	0.3389 (0.05656)	
Difference in LS Means (SE)			0.0388 (0.0431)
Two-sided 95.8% CI of Difference in LS Means			(-0.0565, 0.1340)

Source: Reviewer's Table.
Note: WBC Cystine Levels are measure in nmol/½ cystine/mg protein.
[1]: Obtained by a repeated measures analysis of variance within the linear mixed effects model framework with Treatment Sequence, Period within Treatment Sequence, Treatment and Day utilized as fixed effects. The covariance matrix in this model had a Toeplitz structure.

4.2 Other Special/Subgroup Populations

There were no other special/subgroup populations of interest.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The study design was adequate, and the applicant's corresponding analysis plan was deemed appropriate. A potential statistical issue pertains to the proposed non-inferiority margin. It was not feasible to assess constancy and subsequent assay sensitivity when evaluating the margin from a statistical perspective. This was due to the fact that this margin, and the overall design of RP103-03, was primarily informed by the results of a seven-patient Dohil, Fidler et al. 2010 study as previously described. The margin was deemed acceptable by the clinical review team.

5.2 Collective Evidence

The efficacy of RP103 was primarily demonstrated in trial RP103-03. In this trial, RP103 was demonstrated to be non-inferior to CYSTAGON based on steady-state cysteamine-trough WBC cystine levels. Based on a sustained efficacy profile shown during extension study RP103-04 and with clinical consensus regarding the meaningfulness of the WBC cystine endpoint, there appears to be sufficient evidence to support efficacy claims for RP103. Hence, regarding contribution to overall level of evidence, the RP103-03 trial results are viewed positively as the basis for efficacy claims in the labeling.

5.3 Conclusions and Recommendations

As previously mentioned, there was sufficient evidence to support efficacy claims for RP103, and the claims currently reflected within the applicant's submitted product labeling were validated during this NDA review.

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/s/

BEHRANG VALI
04/26/2013

FREDA COONER
04/26/2013

MICHAEL E WELCH
04/29/2013
Concur with review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 203-389	Applicant: Raptor Therapeutics, Inc.	Stamp Date: 30MAR2012
Drug Name: RP103 (cysteamine bitartrate delayed-release capsules)	NDA/BLA Type: Type 1 NDA; 505(b)(2)	Indication: Management of Nephropathic Cystinosis in Children and Adults

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.			X	This was an electronic submission by the sponsor.
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			This electronic submission was eCTD compliant and of satisfactory quality.
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			There were adequate and complete clinical study reports (CSRs), which were ICH E3 compliant, along with ISE and ISS reports submitted.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).		X		No subgroup analyses for Gender, was presented for the sole adequate and well-controlled study (RP103-03) in this submission. Age and Race subgroup presentations were not necessary as all patients were Caucasian children.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			All data sets provided were of satisfactory quality and were compliant with CDISC data standards. Appropriate data definition files in Define.XML and Define.PDF format were included.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____YES____
If the NDA/BLA is not fileable from the statistical perspective, please state below the reasons and provide comments to be sent to the Applicant.
N/A

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			The designs utilized were adequate.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			The endpoints and methods of analysis were specified in the CSRs including the protocols and Statistical Analysis Plans (SAPs).
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			For the RP103-03 study, there was one interim analysis conducted solely in order to have a more accurate estimate of the primary efficacy variable's variance. This re-estimated variance was subsequently used for an over-all study sample size re-estimation.
Appropriate references for novel statistical methodology (if present) are included.	X			Novel statistical methodology for the sample size re-estimation was referenced.
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			Safety datasets were submitted for each study individually; however this data can be integrated.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			The sponsor's investigation of the effect of dropouts on the statistical analyses was adequate.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please communicate below any additional requests to the Applicant for the 74-day letter.

1. For the RP103-03 study, re-conduct the primary analysis by further adjusting the analysis by the two-level stratification variable used in the randomization (WBC cystine level Group L / WBC cystine level Group H). This re-analysis should be administered separately for the Efficacy Analysis Set and the Per-Protocol Analysis Set. In addition, for further sensitivity analysis purposes, this re-analysis should also be administered on an All-Randomized (n=43) Analysis Set of patients.

2. For the RP103-03 study, present the primary analysis results for the gender subgroups. This analysis should be adjusted by the two-level stratification variable used in the randomization (WBC cystine level Group L / WBC cystine level Group H) and should be administered on an All-Randomized (n=43) Analysis Set of patients.

3. For the RP103-03 study, please submit the SAS programs used to generate the analysis datasets and all efficacy tables found within the finalized RP103-03 Clinical Study Report. These SAS programs should be submitted in their original *.sas format.

4. For the forty RP103-03 patients who enrolled in the RP103-04 study, please provide a figure which plots the mean (± standard deviation) concentration of WBC Cystine over time while these patients are being administered RP103 (Cystagon WBC Cystine levels are not necessary for this figure). Time should range from the beginning of the RP103-03 study (i.e. Randomization) through the point of last data cutoff in the RP103-04 study.

Background

Raptor Therapeutics, Inc. has submitted this New Drug Application (NDA) for RP103 (Cysteamine Bitartrate delayed-release capsules) pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21, Part 314 of the Code of Federal Regulations. The proposed indication for RP103 is for the management of nephropathic cystinosis in children and adults. The reference drug and the basis for the application is CYSTAGON® (NDA 20-392). Since its approval in 1994, CYSTAGON is considered to be the standard therapy for treating patients with nephropathic cystinosis and is the only therapy currently available to treat the disease.

Nephropathic cystinosis is a rare inherited condition which causes the buildup of a protein building block called cystine in every cell of the body. The condition is fatal in early childhood, if not treated, and is thought to affect fewer than 500 patients in the USA. The active ingredient in RP103 (to be administered as a capsule BID) is cysteamine bitartrate. RP103 has undergone clinical development under IND 103,694 in patients with nephropathic cystinosis, and has been developed specifically to establish safety and efficacy in this patient population.

The review cycle established by the Division of Gastroenterology and Inborn Error Products (DGIEP) is a standard 10 month cycle. The application also qualifies for Orphan Exception under section 736(a)(1)(E) of the Federal Food, Drug and Cosmetic Act. Raptor Therapeutics did obtain *Orphan Designation* from the Office or Orphan Products Development (OOPD) on October 24, 2006.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

This NDA was submitted electronically in eCTD format. The submission was sent via the FDA Electronic Submissions Gateway (ESG) and its content along with the electronic data sets and labeling information have been stored in the electronic document room (EDR) at this path location: \\Cdsesub1\evsprod\NDA203389. The submission can consequently be accessed directly at the previous path specified.

Brief Overview and Summary of Relevant Trials

RP103 has been studied by Raptor Therapeutics for the treatment of nephropathic cystinosis, and its clinical efficacy and safety has been principally evaluated through one study: a Phase 3, multicenter, randomized, active controlled, cross-over, non-inferiority study (RP103-03) which serves as the lone adequate and well controlled study of this clinical development program as per 21 CFR 314.126.

The following table presents information on the lone relevant trial contained in the submission.

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety; Phase 3	RP103-03	Demonstrate non-inferiority of RP103 vs. CYSTAGON in reducing WBC cystine	Multicenter, randomized, active controlled, cross-over, non-inferiority	RP103 Q12H followed by Cystagon Q6H OR Cystagon Q6H followed by RP103 Q12H; BID; Oral	Total: 43	Patients with nephropathic cystinosis	8 weeks (3 weeks treatment with RP103 and 5 weeks treatment with CYSTAGON due to 2 week active Run-In period)	Complete; Full

Review Issues

There are no review issues to report at this time.

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/s/

BEHRANG VALI
06/04/2012

MICHAEL E WELCH
06/05/2012