# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203389Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY REVIEW

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| NDA: 203389 | Submission Date: 30 March 2012 |
| Submission Type; Code: | Original |
| Brand/Code Name: | Pending |
| Generic Name: | Cysteamine Bitartrate |
| Primary Reviewer: | Kristina Estes, PharmD |
| Secondary Reviewer | Sue-Chih Lee, PhD |
| PM Reviewer: | Justin Earp, PhD |
| PM Secondary Reviewer | Nitin Mehrotra, PhD |
| OCP Division: | DCP3 |
| OND Division: | DGIEP |
| Sponsor: | Raptor Pharmaceuticals |
| Relevant IND(s): | 103,694 |
| Formulation; Strength(s): | Capsule; 25 mg and 75 mg |
| Proposed Indication: | Treatment of nephropathic cystinosis |
| Proposed Dosage Regimen: | Starting dose:<br>Maintenance dose: |

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# 1 Executive Summary

Cysteamine bitartrate is a delayed-release drug intended for the treatment of nephropathic cystinosis in children and adults. An immediate-release product, Cystagon (NDA 20-392), is approved for this indication and has been marketed in the US since 1994. Nephropathic cystinosis is a genetic disorder affecting approximately 2000 – 3000 patients worldwide and an estimated 500 patients in the US. Cystagon, the standard of care for cystinosis, must be administered every six hours to maintain adequate cystine levels. Cysteamine bitartrate is formulated as enteric coated beads, which may be administered every twelve hours to improve patient compliance. The sponsor seeks to market this drug as a 25 mg and 75 mg capsule in the U.S.

This NDA is submitted under the provisions of 505(b)(2). To support the clinical pharmacology section of this NDA, the sponsor has submitted the results of three Phase 1 studies, a Phase 2 study, and one Phase 3 trial. The Phase 1 studies in healthy volunteers included three single-dose pharmacokinetic (PK) studies, of which one also included an exploration of the food effect. The sponsor has also submitted data from nine in vitro studies.

## 1.1 Recommendations

From the viewpoint of the Office of Clinical Pharmacology, the Clinical Pharmacology and Biopharmaceutics information in the NDA is acceptable provided that mutual agreement on label language can be reached between the sponsor and the Agency.

## 1.2 Phase IV Commitments

None

## 1.3 Summary of CPB Findings

*PK/PD in Cystinosis Patients*

RP103 achieves maximum systemic exposure approximately 3 hours post-dose in cystinosis patients. The mean WBC cystine declines following administration RP103 and closely follows the pharmacokinetics of the drug. Relative to IR Cystagon, there is a slower decline in WBC cystine and a slower return to baseline in WBC cystine compared to RP103 treated patients. The mean WBC cystine levels all remain below 1 nmol/ ½ cystine/mg protein during the 12 hour dosing interval. RP103 is titrated to WBC cystine response; therefore, the dose is highly individualized. Based on the results of Study RP103-03, a phase 2/3 clinical trial, the total daily dose of RP103 should be approximately equivalent to the steady-state dose of Cystagon, when switching from the IR to the DR product.

*Dosing Recommendations*

The pharmacometric reviewer's analysis finds three points to suggest that the starting dose of RP103 should contain the same amount of cysteamine as the patient's maintenance Cystagon® dose:

1. The dose-response analysis suggests that patients who switched to a lower dose of cysteamine bitartrate (70 to 80% of prior Cystagon® dose) with RP103 administration as compared to Cystagon administration had reduced benefit in lowering the concentrations of white-blood-cell (WBC) cystine.

2. The clinical trial data indicate that patients doses were generally increased throughout the trial and a protocol amendment was submitted to increase the RP103 dose patients were to initially receive.

3. Finally, the original proposed label doses and dose amounts administered during the trial were incorrectly determined. After correct analysis of the dosage forms it is apparent that the Cystagon dosage forms contained 85% of the stated dose and the RP103 contained ~91% of the stated dose in the phase III clinical trial. This would suggest that the amounts of cysteamine administered with RP103 are closer to that with Cystagon than initially

anticipated. See the CMC review by Dr. Jane Chang for further details. The corrected dose amounts are used in the reviewer's analysis.

*PK in Healthy Volunteers and Food Effect*
The PK of RP103 in healthy adult volunteers was described in two studies, RP103-05 and RP103-06. The objective of study -05 was to assess two methods of administration (opened vs intact capsules with applesauce) and to address the effect of a small meal administered either 30 minutes or 2 hours post-dose. The results showed that the bioavailability of cysteamine was similar when administered as an intact capsule or sprinkled in applesauce. The food effect portion of the study clearly showed an impact on the PK profile when a meal was administered 30 minutes post-dose but no effect at 2 hours post-dose. Study -06 was conducted to assess the impact of an acidic liquid (orange juice) on the PK profile of opened or intact capsules. The bioavailability appeared to be similar when RP103 was administered with orange juice as an intact capsule or as a sprinkle.

*In vitro Studies*
A variety of in vitro studies were conducted in support of the application including metabolic stability in human liver microsomes (HLM), MAO reaction phenotyping, cytochrome P450 inhibition (multiple systems), cytochrome P450 induction, P-gp affinity, and affinity for transporter uptake. A study using HLM appeared to show low intrinsic clearance. The results of a subsequent study, performed with recombinant CYP enzymes were not considered reliable. The CYP induction study hinted on low induction potential but was not conclusive. Cysteamine does not appear to be an inhibitor of CYP enzymes. The results also suggest that cysteamine is a P-gp substrate but not a BCRP substrate and cysteamine is not an inhibitor of either transporter. Cysteamine is not a substrate of MAO.

# 2 QBR

## 2.1 Background

2.1.1 What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

Cystagon® (cysteamine bitartrate), approved on August 15, 1994 in the USA (NDA 20-392) and is currently the only approved therapy for cystinosis, an inherited defect of lysosomal transport. Cystagon® is available as 150 mg or 50 mg immediate-release capsules for oral administration. Cystagon must be administered every six hours to maintain white blood cell (WBC) cystine levels below the threshold of 1-2 nmol/ ½ cystine/mg protein. In clinical practice, patients are typically titrated to an appropriate, individualized dose. To address concerns related to compliance with the strict Q6H dosing regimen, Raptor developed a delayed-release formulation of cysteamine bitartrate to be given on a Q12H schedule for the treatment of cystinosis. Cysteamine bitartrate delayed-release capsules (RP103) contain either 25 or 75 mg of cysteamine free base formulated in microspheronized (b) (4) beads (b) (4) that are subsequently enteric-coated.

The application for cysteamine bitartrate delayed-release capsules has been submitted as a 505(b)(2), partially relying on previous findings of safety and efficacy for Cystagon. The sponsor has submitted six clinical studies and nine in vitro studies in support of their application.

2.1.2 List the *in vitro* and *in vivo* clinical pharmacology and biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA.

Three clinical pharmacology studies were performed in healthy volunteers and three studies were performed in cystinosis patients. The following table lists the clinical studies that were submitted in support of this application.

Table 1. Summary of Clinical Pharmacology Studies

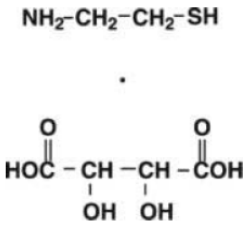
| Study Identifier | Type of Study | Number of subjects | Duration of treatment | Patient Population |
|---|---|---|---|---|
| RP103-01 | PK/PD | 9 | 1 day | Adult and pediatric patients |
| RP103-02 | PK | 22 | 1 day | Healthy volunteers |
| RP103-03 | PK/PD | 43 | 21 days | Adult and pediatric patients |
| RP103-04 | Safety | 48 | | Adult and pediatric patients |
| RP103-05 | Food effect | 20 | 1 day | Healthy volunteers |
| RP103-06 | Food effect | 20 | 1 day | Healthy volunteers |

In addition, the following in vitro studies were conducted in support of the application: metabolic stability in human liver microsomes, MAO reaction phenotyping, cytochrome P450 inhibition (multiple systems), cytochrome P450 induction, P-gp affinity, and affinity for transporter uptake.

## 2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

The molecular formula is $C_2H_7NS \cdot C_4H_6O_6$ with a molecular weight of 227.24 Da. The molecular weight of the free base is 77.15 Da. Cysteamine bitartrate is a white powder and is freely soluble in water. The chemical structure of cysteamine bitartrate is provided below:



Raptor's Cysteamine Bitartrate Delayed-release Capsules (RP103) contain either 25 or 75 mg of cysteamine free base formulated in microspheronized (b) (4) beads that are subsequently enteric coated (b) (4) The enteric-coated (b) (4) beads are encapsulated in size 3 (25 mg strength) or size 0 (75 mg strength) blue hard gelatin capsules. The primary reason for developing RP103 was to improve patient compliance. The beaded encapsulated formulation was chosen to permit patients who cannot or have difficulty swallowing the capsules to be able to sprinkle the contents of the capsule on soft food or liquid.

2.2.2 What are the proposed mechanism of action and therapeutic indication(s)?

Cystinosis is an autosomal recessive inborn error of metabolism in which the transport of cystine out of lysosomes is abnormal. Accumulation of cystine and formation of crystals damage various organs, especially the kidney, leading to renal tubular Fanconi Syndrome and progressive glomerular failure, with end stage renal failure by the end of the first decade of life. Cysteamine is an aminothiol that participates within lysosomes in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide, both of which can exit the lysosome in patients with

cystinosis. Cystagon and cysteamine bitartrate delayed-release capsules are indicated for management of nephropathic cystinosis in children and adults.

2.2.3 What are the proposed dosage and route of administration?

The RP103 capsule may be swallowed whole or may be opened and sprinkled over food or liquid. The starting dose (new diagnosis of cystinosis) is recommended to be 1/4 to 1/6 of the maintenance dose of RP103. The dose should be raised gradually over 4 to 6 weeks to avoid side-effects. Leukocyte cystine measurements, taken ½ hour after dose administration, are recommended for new patients after the maintenance dose is achieved. According to the sponsor, the recommended RP103 maintenance dose (b) (4) in two divided doses, given every 12 hours. The recommended maintenance dose of (b) (4) can be approximated by administering RP103 (b) (4) which takes surface area as well as weight into consideration.

(b) (4)

In clinical practice, the dose of cysteamine is titrated to achieve a WBC cystine level below 1-2 nmol/½ cystine/mg protein. This proposed maintenance dose appears to be adopted from the current Cystagon label with the primary difference being that the dosing values have been multiplied by 0.7 based on the early assumption that exposure following RP103 administration was greater than an equivalent oral dose of Cystagon. However, the pharmacometric reviewer disputes this conclusion and has recommended a straight conversion. The lowest age group that is proposed to be included in the label is six years of age, (b) (4)

The proposed dosing for patients (b) (4) every 12 hours, titrated every 4-6 weeks to achieve the WBC cystine goal.

2.2.4 What drugs with the same indication are approved in the U.S.?

The only other product approved for the management of nephropathic cystinosis in the US is Cystagon.

## 2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The sponsor performed three clinical pharmacology studies in healthy volunteers and three studies in cystinosis patients. See table below.

Table 3. Summary of clinical studies including healthy volunteers and patients

| Study Identifier | Type of Study | Objective of study | Duration of treatment | Demographics (n) |
|---|---|---|---|---|
| RP103-01 | PK/PD | Safety and tolerability; inform design of RP103-03 (pivotal study) | 1 day | Adult and pediatric patients (9) |
| RP103-02 | PK | Demonstrate BE of intact vs opened capsule in fed state | 1 day | Healthy volunteers (22) |
| RP103-03 | PK/PD | Demonstrate non-inferiority of RP103 vs Cystagon | 9 weeks | Adult and pediatric patients (43) |
| RP103-04 | Safety | Demonstrate non-inferiority of RP103 vs Cystagon | Up to 24 months | Adult and pediatric patients (48) |
| RP103-05 | Food effect | Demonstrate BE of intact vs opened capsule and PK following meal delay | 2 weeks | Healthy volunteers (20) |
| RP103-06 | Food effect | Demonstrate BE of intact vs opened capsule | 2 weeks | Healthy volunteers (20) |

2.3.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Normal individuals and persons heterozygous for cystinosis have white cell cystine levels of < 0.2 and usually below 1 nmol/ ½cystine/mg protein, respectively. Individuals with nephropathic cystinosis have elevations of white cell cystine above 2 nmol/ ½ cystine/mg protein. WBC cystine is monitored 5 to 6 hours after dosing in these patients to determine adequacy of dosing. After administration of Cystagon (IR), leukocyte cystine levels fall, with minimum levels at approximately 1 hour.

2.3.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, see Analytical Section.

## 2.4 Exposure-response

2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

Cysteamine bitartrate is a cystine depleting agent which lowers the cystine content of cells in patients with cystinosis, an inherited defect of lysosomal transport. The clinical efficacy of cysteamine treatment in cystinosis patients is determined by monitoring the white blood cell (WBC) cystine levels several hours post-dose. In clinical practice, patients are typically titrated to an appropriate, individualized dose.

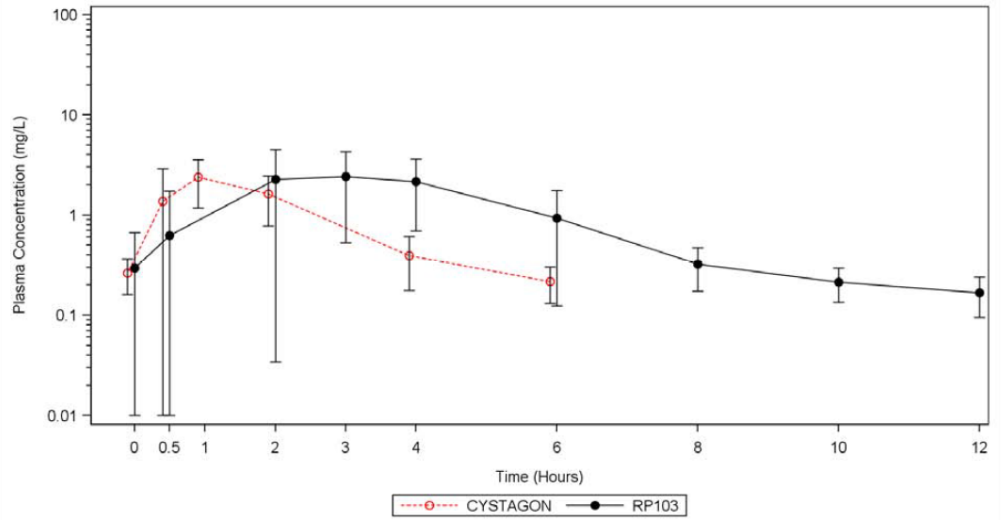
Study RP103-03, conducted in pediatric and adult cystinosis patients, explored the relationship between cysteamine dose and WBC cystine. The primary objective of the study was to demonstrate adequate response at steady-state to RP103 administered every twelve hours compared to Cystagon administered every six hours in depletion of WBC cystine. The study consisted of a 2 to 3 week run-in period of Cystagon treatment followed by two treatment periods: Period 1 (Weeks 4 to 6; ±3 days) and Period 2 (Weeks 7 to 9; ±3 days). Subjects were stratified based on their level of WBC cystine during the run-in period: Group L ≤1.0 nmol/ ½ cystine/mg protein; Group H >1.0 ≤ 2.0 nmol/ ½ cystine/mg protein).

This study included patients maintained on an individualized Cystagon dose (administered Q6H) sufficient to meet WBC cystine goals; therefore, the actual dose administered to study participants was not fixed. The mean baseline Cystagon dose was approximately 1800 mg/$m^2$/day (SD 511) with a range of 982 to 3000 mg/$m^2$/day. The mean age of participants was 11.9 years with a range of 6 to 26 years of age. Of the 38 patients, 22 (57.9%) were male and 16 (42.1%) were female. All but one patient was classified as White.

During the Run-in and Periods 1 and 2 clinic days, patients were provided with a small meal or snack 30 minutes prior to study drug administration and swallowed the administered dose with the protocol prescribed beverage. This study design differs from the food effect studies (-05 and -06) in which the meal was administered 30 minutes or two hours post-dose.

At the end of Period 1, subjects immediately crossed over to the opposite treatment for 3 weeks (Period 2). Subjects receiving Cystagon every 6 hours during Period 1 were switched to RP103 every 12 hours and subjects receiving RP103 every 12 hours were switched to Cystagon every 6 hours. The starting daily dose of RP103 for Periods 1 and 2 was 70-80% of the total daily dose of Cystagon during the run-in period. During either Week 5 (Period 1) or Week 8 (Period 2), while subjects were taking RP103, the dose could be increased to approximately 92-100% of the total daily dose of Cystagon depending on WBC cystine levels and safety data review.

Figure 1. Mean Plasma Cysteamine Concentrations versus Time During the Dosing Interval in Study RP103-03




The figure above shows the difference in plasma PK profile between the IR product (in red) and the delayed-release product (in black). The mean $C_{max}$ appears to be similar between the two products but the $t_{max}$ for the IR product occurs 1.5 to 3.5 hours earlier than the DR product. The $C_{max}$ for the DR product appears to be sustained for approximately two hours while the plasma concentration of the IR product rapidly declines.

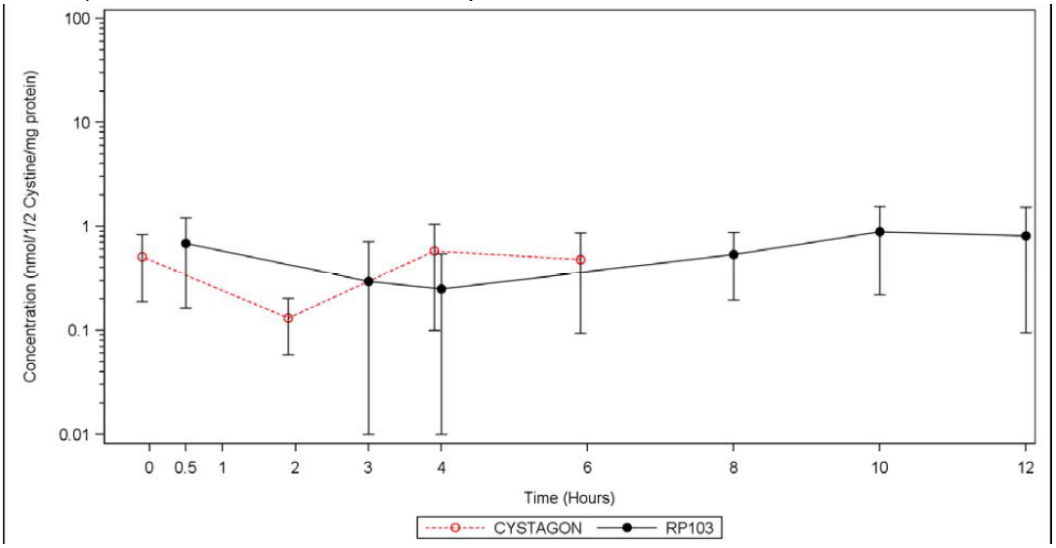
Table 4. Statistical Analysis of Pharmacodynamic Parameters of WBC Cystine (nmol ½ Cystine/mg protein) in the Per Protocol Population

| Treatment | N | LS Means (SE) | Difference of LS Means[1] (SE) | SE of LS Mean Difference | T-Value for CI (DF=37) | 95.8% CI[2] of LS Means Difference[1] | T-Statistic Associated P-Value |
|---|---|---|---|---|---|---|---|
| **Cystagon®** | 38 | 0.5424 (0.05287) | 0.0809 | 0.0415 | 2.1057 | (-0.0065 to 0.1683) | <0.0001 |
| **RP103** | 38 | 0.6233 (0.05295) | | | | | |

LS=least squares; SE=standard error; DF=degree of freedom; CI=confidence interval
[1] RP103 LS means minus Cystagon® LS means
[2] The alpha level used for the final analysis (a one-sided test) was 0.02104. This alpha-level corresponds to a 97.896% one-sided confidence interval of the parameter of interest (i.e. 95.8% 2-sided CI).
Note: The non-inferiority margin of 0.3 was used in this study. The null hypothesis of inferiority will be rejected in favor of non-inferiority if the on-sided p-value is less than or equal to 0.02104.

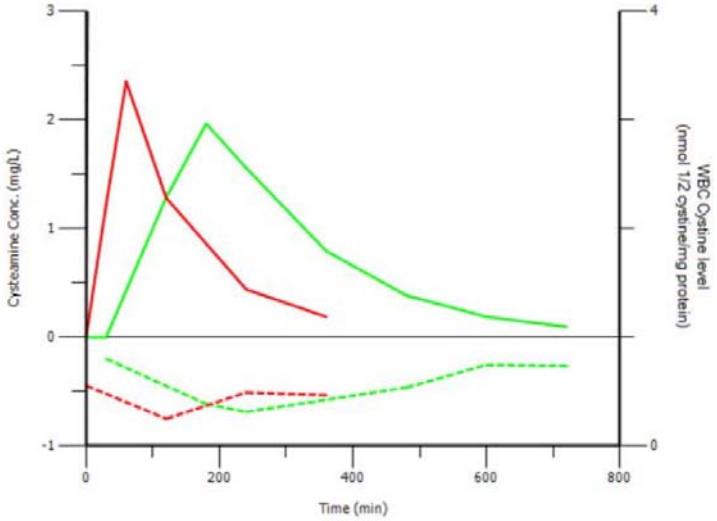
Mean WBC cystine is increased by approximately 20% in patients who received RP103 for three weeks relative to patients who received Cystagon for three weeks but the difference is not statistically significant. These patients were on a stable (steady-state) dose of Cystagon prior to enrollment in the study and the dose of RP103 was estimated to provide similar plasma exposure while simplifying the dosing regimen from four times daily to twice daily. It appears that the dose of RP103 necessary to achieve exposure comparable to Cystagon was not clearly established prior to the start of this study. However, the pharmacokinetics of the two products are quite different and the pilot studies conducted to elucidate the PK/PD relationship between the two products included a small number of patients. Administration of both products results in WBC cystine levels that are considered acceptable based on a published report by the European Research Network for Evaluation and Improvement of Screening, Diagnosis and Treatment of Inherited Disorders of Metabolism.

Figure 2. Mean (±SD) Concentrations of WBC Cystine (nmol/ ½ Cystine/mg Protein) vs. Time in the Per Protocol Population




The mean WBC cystine declines following administration of either Cystagon or RP103 and the declines closely follow the pharmacokinetics of each drug. There is a more rapid decline in the Cystagon group followed by a faster increase in WBC cystine relative to RP103 treated patients. The mean levels all remain below 1 nmol/ ½ cystine/mg protein during the dosing interval (6 hours for Cystagon and 12 hours for RP103).

Figure 3. Mean WBC Cystine versus Mean Plasma Cysteamine Exposure




The figure above shows both the mean plasma cysteamine exposure and the corresponding mean WBC cystine together on a linear scale. As noted above, the decline in WBC cystine closely follows the increase in plasma cysteamine concentrations in patients with the minimum WBC cystine occurring shortly after the plasma cysteamine $C_{max}$.

2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Patient exposure to cysteamine over a 24 hour period would be significantly reduced following Q12H treatment with RP103 relative to Q6H treatment with Cystagon while maintaining sufficient reduction in WBC cystine over the same period. The $C_{max}$ following administration of RP103 is sustained for approximately 2 hours while the $C_{max}$ of Cystagon rapidly declines; however, there does not appear to be any correlation between the sustained levels of plasma cysteamine and the occurrence of adverse events.

2.4.3 Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The sponsor has proposed dosing for maintenance treatment by weight (b) (4) group (see Table 2). (b) (4) every 12 hours. These recommended RP103 doses are approximately 70% of the total daily dose of Cystagon; however, the Agency recommends patients switching from Cystagon to RP103 be administered the same total daily dose of cysteamine based on an analysis of the clinical trial data. Please refer to the pharmacometric review by Dr. Justin Earp in Appendix 4.1 for details.

The recommendation for an initial (treatment naïve) starting dose of RP103 is ¼ to 1/6 of the maintenance dose, raised gradually over 4 to 6 weeks to avoid side-effects. The clinical trials that were conducted in support of the application did not include treatment naïve patients; however, given the drug is titrated individually based on a widely accepted biomarker, it may be reasonable to administer RP103 in these patients.

## 2.5 Pharmacokinetics

2.5.1 What are the single dose and multiple dose PK parameters?

The single-dose PK parameters were assessed in three studies using healthy adult volunteers. Unfortunately, in the first of these studies (RP103-02), the PK parameters were not able to be described due to a significant food effect. In studies RP103-05 and -06, volunteers were administered a single, fixed dose of the delayed-release product as an intact capsule or opened and the contents sprinkled over a food or mixed with a specified liquid. No multiple dose data was collected in healthy volunteers. The design of studies RP103-05 and -06 were very similar; however, study RP103-05 also included a sub-study to explore the food effect (see 2.8.3 for a discussion of the food effect).

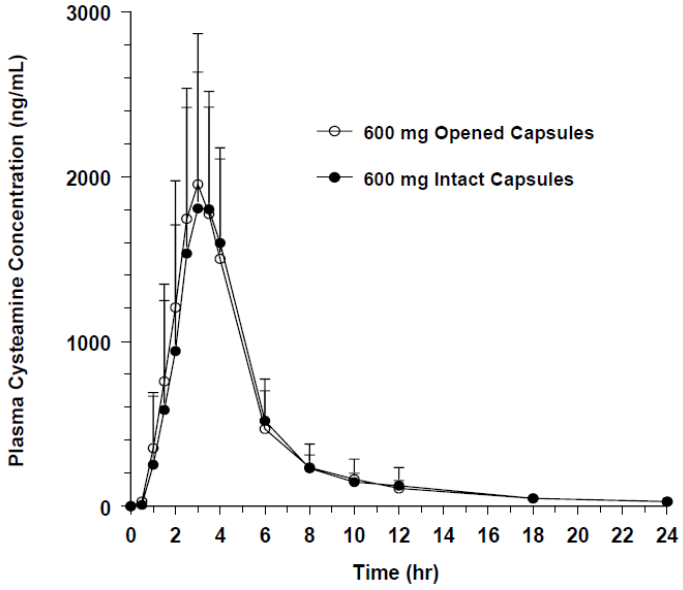
*Study RP103-05*

This was a single-center, open-labeled, randomized, 2-period, 2-sequence, crossover design study to evaluate the bioequivalence of 2 different modes of administration of RP103 following a 600 mg dose in healthy subjects under fasted conditions. Dosing for Treatment A was delivered in four ounces of applesauce. Not more than 30 minutes before dosing, the pharmacist opened the 8 capsules of study drug and poured the content of each capsule into the applesauce. For Treatment B, subjects were instructed to swallow the capsules intact with water until all 8 capsules were consumed. Then the subjects were instructed to drink the remaining water for a total of 240 mL. If extra water was needed, the amount of additional water was recorded. Each subject in Treatment B (intact capsules) also consumed four ounces of applesauce, a design variable which is not generally recommended by the Agency for assessing the bioavailability of drug products when administered as a sprinkle.

The crossover BE portion of the study used a sequential design in which an interim analysis was planned after Stage 1 (20 subjects). If bioequivalence or non-bioequivalence was concluded at that time, then the study was to be stopped. If bioequivalence was not concluded at Stage 1, but the observed ratios for AUC or $C_{max}$

were within 0.80 to 1.25, the study would proceed with Stage 2. Stage 2 was to be conducted at the same clinical site as Stage 1 and the same protocol requirements and procedures were to be followed. Interim analysis after Stage 1 showed bioequivalence with the 94.12% geometric confidence intervals for the ratio of the least-squares means for ln-transformed $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$ and $C_{max}$ all within 0.80 to 1.25. Therefore Stage 2 was of the study was not conducted.

Figure 4. Mean Plasma Cysteamine Concentration Following a Single Dose of 600 mg RP103 Administered as Intact Capsules or Sprinkled on Applesauce.




The PK profile for cysteamine appears similar when administered as an intact capsule with applesauce or administered as a sprinkle mixed with applesauce. The $t_{max}$ in both groups occurs at approximately three hours and the rate of absorption is similar in both groups.

Table 5. Pharmacokinetic Parameters Following a Single 600 mg Dose of RP103 Administered as Intact Capsules or Sprinkled on Applesauce in study RP103-05.

| | Crossover (N=19) | |
|---|---|---|
| **Pharmacokinetic Parameter** | **RP103 Opened Capsules Treatment A** | **RP103 Intact Capsules Treatment B** |
| $AUC_{(0\text{-}t)}$ (hr·ng/mL) | 7965 (1984) | 7795 (1779) |
| $AUC_{(0\text{-}inf)}$ (hr·ng/mL) | 8197 (2049) | 8039 (1848) |
| fext (%) | 2.82 (0.552) | 2.99 (0.609) |
| $C_{max}$ (ng/mL) | 2316 (718) | 2268 (576) |
| $T_{max}$ (hr)[a] | 3.00 (1.50 – 6.00) | 3.00 (2.00 – 4.00) |
| t ½ (hr) | 6.06 (0.970) | 6.08 (0.840) |

Source: Section 14, Table 14.7.6.
Abbreviations: hr = hour; N = number of subjects, SD = standard deviation.
[a] Median (range).

The plasma cysteamine exposure is similar when administered as intact capsules or sprinkled over applesauce. The median $t_{max}$ in both groups is 3 hours although there is a wide range in both groups. The $t_{½}$ is approximately six hours in both groups.

Table 6. Statistical Analysis of Pharmacokinetic Parameters in Period 1 (Crossover BE)

| Parameter | Geometric Mean Ratio (A/B) | 94.12% Confidence Interval for Ratio of Least-Squares Means |
|---|---|---|
| Geometric AUC(0-t) | 1.012 | 0.959–1.069 |
| Geometric AUC(0-inf) | 1.010 | 0.957–1.067 |
| Geometric Cmax | 0.999 | 0.885–1.127 |

The GMRs and confidence intervals for both $C_{max}$ and AUC show bioequivalence between the intact capsule and the contents of the opened capsules mixed with applesauce.

*Study RP103-06*

This was a single-center, open-labeled, randomized, 2-period, 2-sequence, crossover design study to evaluate the bioequivalence of 2 different modes of administration of RP103 following a 600 mg dose in healthy subjects under fasted conditions. Treatment A (opened capsules) was delivered in four ounces of applesauce. Once all the applesauce was consumed, subjects were instructed to drink 240 mL of orange juice. For Treatment B, subjects were instructed to swallow the capsules intact with 240 mL of orange juice until all 8 capsules were consumed. The primary difference between this study and RP103-05 was the addition of the orange juice in both treatment groups and the absence of applesauce in the intact capsule group. In addition, this RP103-06 was not a sequential design but rather included previous estimates of intrasubject variability to determine the sample size for this BE study. Blood samples for plasma cysteamine were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18, and 24 hours post-dose.

Table 7. Pharmacokinetic parameters following a single 600 mg dose of RP103 administered as intact capsules with orange juice or sprinkled on applesauce in study RP103-06.

| | Crossover (N=19) | |
|---|---|---|
| Pharmacokinetic Parameter | RP103 Opened Capsules Treatment A | RP103 Intact Capsules Treatment B |
| AUC(0-t) (hr·ng/mL) | 6795 (1868) | 6868 (1695) |
| AUC(0-inf) (hr·ng/mL) | 7001 (1918) | 7087 (1757) |
| fext (%) | 2.96 (0.583) | 3.07 (0.682) |
| Cmax (ng/mL) | 2074 (615) | 2157 (415) |
| Tmax (hr)[a] | 3.50 (1.00 – 4.00) | 3.50 (2.00 – 4.00) |
| t ½ (hr) | 5.78 (0.671) | 5.86 (0.817) |

Source: Section 14, Table 14.7.2.
Abbreviations: hr = hour; N = number of subjects, SD = standard deviation.
[a] Median (range).

Plasma cysteamine exposure is very similar following administration of RP103 as intact capsules or sprinkled over applesauce. In this study, 240 mL orange juice was given to all subjects including those who received RP103 sprinkled in applesauce. The study appears to have been conducted based on feedback from the Agency regarding the impact of acidic beverages and the impact on labeling for the proposed product. To test the impact of acidic beverages on bioavailability, ideally, subjects would have received intact capsules with and without the acidic beverage. In this study, all subjects received the acidic beverage but some were administered intact capsules and others were administered the contents of opened capsules with applesauce. Exposure to RP103 in this study was up to 15% lower than exposure in Study RP103-05, in which there were differences in study design. Study RP103-05 included the following: 1) water (no acidic beverage) was administered with the study drug, and 2) applesauce was administered to the intact capsule group. However, the value of such a cross-study comparison is unknown.

2.5.2 How does the PK of the drug in healthy volunteers compare to that in patients?

The PK of RP103 was characterized in pediatric and adult patients; however, data collected in the proof-of-concept study (RP103-01) included many amendments related to study drug administration or dosing that preclude a meaningful assessment of the study results. Study RP103-03 provided the best estimate of PK parameters in cystinosis patients. The studies performed by the sponsor in cystinosis patients did not include a fixed dose but were designed to provide a roughly equivalent dose of the delayed-release product to patients maintained on a steady dose of the IR product. A comparison of the PK between healthy volunteers and patients is complicated by the differences in dosing among patients, the demographic differences between the patient population and volunteers, and the availability of only single-dose data in healthy volunteers and only multiple-dose data in patients.

*PK data in cystinosis patients*: *Study RP103-03*
This was a randomized, crossover, outpatient study of the safety, efficacy, tolerability, PK and PD of RP103 in pediatric and adult subjects with nephropathic cystinosis. Patients on a stable dose of Cystagon, considered sufficient to maintain their WBC cystine level at ≤2.0 nmol ½ cystine/mg protein, were eligible for enrollment in the study.
The study consisted of two treatment periods: Period 1 (Weeks 4 to 6; ±3 days) and Period 2 (Weeks 7 to 9; ±3 days) preceded by a 2 to 3 week run-in period of Cystagon treatment. Subjects were stratified based on their level of WBC cystine during the run-in period: Group L ≤1.0 nmol ½ cystine/mg protein; Group H >1.0 ≤2.0 nmol ½ cystine/mg protein). Subjects 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, if possible.

At the end of Period 1, subjects immediately crossed over to the opposite treatment for 3 weeks (Period 2). Subjects receiving Cystagon every 6 hours during Period 1 were switched to RP103 every 12 hours and subjects receiving RP103 every 12 hours were switched to Cystagon every 6 hours. The starting daily dose of RP103 for Periods 1 and 2 was 70-80% of the total daily dose of Cystagon during the run-in period. During either Week 5 (Period 1) or Week 8 (Period 2), while subjects were taking RP103, the dose could be increased to approximately 92-100% of the total daily dose of Cystagon depending on WBC cystine levels and safety data review.

Blood samples for plasma cysteamine exposure were collected as follows:

<u>All subjects</u>
Week 2, Days 3, 4 and 5: one blood sample was drawn within 15 minutes pre-dose
<u>Cystagon treated subjects</u>

Week 4 or 7; Days 3, 4 & 5: one blood sample was drawn within 15 minutes pre-dose;
Week 6 or 9; Days 5 & 6: one blood sample was drawn within 15 minutes pre-dose;
Week 6 or 9, Day 7: samples were drawn within 15 minutes pre-dose and at 0.5, 1, 2, 4 and 6 hours post-dose
RP103 treated subjects
Week 4 or 7; Days 3, 4 & 5: one blood sample was drawn 0.5 hour post-dose;
Week 6 or 9; Days 5 & 6: one blood sample was drawn 0.5 hour post-dose;
Week 6 or 9; Day 7: blood samples were drawn within 15 minutes pre-dose and at 0.5, 2, 3, 4, 6, 8, 10 and 12 hours post-dose

Table 8. Pharmacokinetic Parameters (AUC and $C_{max}$) on Day 7 in the Per Protocol Population

| Parameter/ Treatment | N | LS Means[3] | Difference in LS Means (RP103-Cystagon®) | 95% CI of Ratio (RP103-Cystagon®) | Intra-subject CV% |
|---|---|---|---|---|---|
| **$AUC_{(0-t)}$ (min*mg/L)** | | | | | |
| **Cystagon®[1]** | 38 | 5.78 | 0.72 | 1.74 to 2.40 | 34.82 |
| **RP103[2]** | 36 | 6.50 | | | |
| **$AUC_{(0-\infty)}$ (min*mg/L)** | | | | | |
| **Cystagon®** | 38 | 5.87 | 0.71 | 1.75 to 2.37 | 32.44 |
| **RP103** | 36 | 6.58 | | | |
| **$C_{max}$ (mg/L)** | | | | | |
| **Cystagon®** | 38 | 0.86 | 0.33 | 1.15 to 1.67 | 40.48 |
| **RP103** | 36 | 1.19 | | | |

LS=least squares; CI=confidence interval; CV=coefficient of variation
[1] $AUC_{(0-t)}$ for Cystagon® was calculated based on cysteamine blood levels at each timepoint up to 6 hours post dosing on Day 7 of Week 6 or Week 9.
[2] $AUC_{(0-t)}$ for RP103 was calculated based on cysteamine blood levels at each timepoint up to 12 hours post dosing on Day 7 of

Plasma cysteamine exposure at steady-state is similar between patients treated with Cystagon every six hours and RP103 every 12 hours.

2.5.3 What are the characteristics of drug absorption?

Compared to the rapid absorption of cysteamine following administration of Cystagon, absorption following administration of RP103 capsules is slower with $t_{max}$ occurring at approximately 2-4 hours post-dose. The $C_{max}$ and $AUC_{0-t}$ are similar between the IR and DR products.

2.5.4 What are the characteristics of drug metabolism?

A variety of in vitro studies were conducted to characterize the metabolism of cysteamine bitartrate. The results are described individually below.

*Human Liver Microsomes*
The in vitro metabolic stability of cysteamine bitartrate in human liver microsomes (HLM) was evaluated. Cysteamine bitartrate (3 µM) was incubated with pooled HLM (0.5 mg protein/mL) in phosphate buffer (100 mM, pH 7.4) containing MgCl2 (5 mM) in the presence and absence of NADPH (1 mM). After a period of incubation, the samples were treated by the addition of protein precipitation solvent (acetonitrile) and centrifuged. The disappearance of cysteamine bitartrate was analyzed by LC-MS/MS, and the half-life and intrinsic clearance were estimated.

Table 9. Metabolic stability of cysteamine bitartrate in HLM.

| Test Compound | Treatment | Measurement | % Remaining of Initial (n=3)[a] | | | | | Half-life[b] (min) | $CL_{int}$[c] (mL/min/mg protein) |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0 min | 10 min | 20 min | 30 min | 60 min | | |
| Cysteamine Bitartrate | +NADPH | Average | 100 | 99.0 | 90.8 | 75.8 | 68.3 | >60 (99) | 0.014 |
| | | SD | 6.3 | 12 | 3.7 | 12 | 14 | | |
| | -NADPH | Average | 100 | | | | 88.0 | ND | ND |
| | | SD | 3.18 | | | | 4.17 | | |

a Percent remaining of test compound was calculated based on the concentration of the test compound measured using a standard curve by LC-MS/MS. Data were expressed as the average of triplicate experiments.
b Half-life was calculated based on $t_{1/2} = 0.693/k$, where k is the elimination rate constant based on the slope of the plot of natural logarithm percent remaining versus incubation time. When the percent remaining was >50% at the maximum incubation time, the half-life was expressed as > the longest incubation time. The calculated half-lives are also listed in parentheses.
c Intrinsic clearance ($CL_{int}$) was calculated based on $CL_{int} = k/P$, where k is the elimination rate constant and P is the protein concentration in the incubation.
ND not determined.

After 60 minutes of incubation with HLM, the percent remaining of cysteamine bitartrate was 68.3% in the presence of NADPH and 88.0% in the absence of NADPH indicating cysteamine is not primarily metabolized by HLM. The half-life of cysteamine bitartrate in HLM in the presence of NADPH was > 60 minutes and the estimated intrinsic clearance was 0.014 mL/min/mg protein.

Table 10. Metabolic stability of testosterone in HLM as a positive control.

| Species | % Remaining of Testosterone (n=1)[a] | | | | Half-life[b] (min) | $CL_{int}$[c] (mL/min/mg protein) | Acceptable Range ($t_{1/2}$, min) |
|---|---|---|---|---|---|---|---|
| | 0 min | 10 min | 30 min | 60 min | | | |
| Human | 100 | 69.4 | 38.2 | 11.4 | 19 | 0.072 | ≤28 |

a Percent remaining of testosterone was calculated based on the peak area ratio of testosterone to the internal standard by LC-MS/MS.
b Half-life was calculated based on $t_{1/2} = 0.693/k$, where k is the elimination rate constant based on the slope of the plot of natural logarithm percent remaining versus incubation time.
c Intrinsic clearance ($CL_{int}$) was calculated based on $CL_{int} = k/P$, where k is the elimination rate constant and P is the protein concentration in the incubation.

The activity of the HLM enzymes used in this study was verified in parallel by determining the disappearance of testosterone (5 µM), a CYP 3A4 substrate. The results of the study demonstrate that testosterone was significantly metabolized, indicating that the HLM used in this study were metabolically active.

*Recombinant CYP enzymes*
Cytochrome P450 (CYP) reaction phenotyping of cysteamine bitartrate (1 µM) was performed using human recombinant CYP enzymes (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) by an in vitro intrinsic clearance approach. The CYP reaction phenotyping using human recombinant CYP enzymes (20 pmol P450/mL) appeared to suggest that cysteamine bitartrate was likely to be metabolized by multiple CYP enzymes, including 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1; however, the results of this study may not be reliable (see discussion below Table 11). CYPs 2A6 and 3A4 were not involved in the metabolism of cysteamine bitartrate under the experimental conditions.

Table 11. Cytochrome P450 reaction phenotyping using recombinant human CYP enzymes.

| CYP | % Remaining of Test Compound (n=1)[a] | | | | | Raw $CL_{int}$[b] | Normalized $CL_{int}$[c] | Corrected $CL_{int}$[d] | Scaled $CL_{int}$[e] | Contribution[f] (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 min | 5 min | 10 min | 15 min | 30 min | | | | | |
| CYP1A2 | 100 | 63.0 | 67.4 | 53.2 | 66.1 | 0.501 | 51.1 | 51.1 | 24.3 | 15 |
| CYP2B6 | 100 | 60.4 | 66.0 | 63.1 | 55.1 | 0.731 | 56.3 | 56.3 | 18.3 | 11 |
| CYP2C8 | 100 | 50.9 | 56.4 | 60.6 | 66.1 | 0.291 | 69.3 | 69.3 | 12.8 | 7.7 |
| CYP2C9 | 100 | 52.4 | 48.7 | 54.1 | 51.8 | 0.727 | 280 | 280 | 61.4 | 37 |
| CYP2C19 | 100 | 36.7 | 43.2 | 69.4 | 38.7 | 0.894 | 256 | 256 | 14.8 | 8.9 |
| CYP2D6 | 100 | 62.7 | 63.2 | 69.5 | 63.4 | 0.482 | 52.3 | 52.3 | 4.33 | 2.6 |
| CYP2E1 | 100 | 17.1 | 18.9 | 101 | 36.6 | 0.549 | 136 | 136 | 30.2 | 18 |
| CYP3A4 | 100 | 94.5 | 89.3 | 100 | 101 | ND | 0 | 0 | 0 | 0 |
| Negative Control | 100 | 292 | 88.6 | 105 | 118 | ND | | | | |
| CYP2A6 | 100 | 91.1 | 98.8 | 105 | 93.5 | 0.038 | 2.91 | 0 (-54) | 0 | 0 |
| Negative Control (CYP2A6) | 100 | 93.9 | 86.5 | 112 | 79.7 | 56.7 | | | | |

a The % remaining of test compound was calculated based on the peak area of the test compound by LC-MS/MS.
b The intrinsic clearance ($CL_{int}$) was calculated based on the goodness of fit to the elimination kinetics and was expressed as µL/min/pmol P450 based on the incubation condition with hrCYP at 20 pmol P450/mL or µL/min/mg Supersome protein for the negative controls (insect control , 0.1 mg protein/mL). The underscored results were excluded from the calculation of intrinsic clearance. When $CL_{int}$ was not detectable (due to the percent remaining of the test compound being ≥100% or not detectable using an elimination equation), the value of raw $CL_{int}$ was reported and treated as zero. ND, not detectable.
c The intrinsic clearance ($CL_{int}$) was normalized and expressed as µL/min/mg Supersome protein, based on the Supersome protein levels of hrCYP (equivalent to 20 pmol P450/mL). No clearance was reported as zero.
d Corrected $CL_{int}$ = normalized $CL_{int\ (hrCYP)} - CL_{int\ (Negative\ Control)}$. No clearance was reported as zero.
e Scaled $CL_{int}$ was calculated based on the individual CYP abundance in HLM, and expressed as µL/min/mg liver microsomal protein. No clearance was reported as zero.
f Percent contribution (rank order) = 100 x [$CL_{int}$ of an individual CYP enzyme x CYP Abundance in HLM/Σ ($CL_{int}$ x CYP Abundance)] =100 x [Scaled $CL_{int}$ of an individual CYP enzyme/ Σ (Scaled $CL_{int}$ of all responsible CYP

In the recombinant systems demonstrating cysteamine metabolism, it appeared to occur rapidly, within the first five minutes of the initiation of the reaction. There does not appear to be significant additional metabolism beyond the first five minutes under these experimental conditions. The sponsor did not explain these unusual results in their study report; therefore, the results cannot be considered reliable at this time. These results should be viewed in the context of the results of the HLM study, which showed very little metabolism.

*MAO metabolism*
Monoamine oxidase (MAO) reaction phenotyping of cysteamine bitartrate (3 µM) was performed using human recombinant MAO enzymes (MAO-A, MAO-B, and control without the expression of MAO) by an in vitro intrinsic clearance approach. After 30 minutes of incubation with MAO enzymes, no decline of cysteamine bitartrate was observed in the incubation samples with either MAO-A, MAO-B, or the control, suggesting that cysteamine bitartrate is unlikely to be metabolized by MAO enzymes in vitro.

2.5.5 What are the characteristics of drug excretion?

The characteristics of drug excretion were not explored.

2.5.6 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Healthy volunteers were administered only one dose level of cysteamine delayed-release capsules (600 mg) in the phase 1 studies. Patients were administered a dose of cysteamine delayed-release capsules that was roughly equivalent to their steady state Cystagon dose. These patients ranged widely in age, body weight, etc. therefore, the dose linearity of the test product was not determined.

2.5.7 How do the PK parameters change with time following chronic dosing?

Healthy volunteers were only administered single doses of RP103; therefore, the change in PK parameters with multiple doses was not able to be assessed. Patients were treated with RP103 for up to three weeks but a comparison of single- and multiple-dose PK was not performed due to the variability in dosing.

## 2.6 Intrinsic Factors

2.6.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

There were no studies conducted to specifically investigate the impact of gender, body weight, ethnicity, race, renal impairment, or hepatic impairment on the PK of RP103. Pediatric patients were included in the clinical trial but the dose of RP103 is typically titrated to a response and not dosed based on intrinsic factors.

2.6.1.1 Pediatric patients. What is the status of pediatric studies and/or any pediatric plan for study?

The current submission appears to support use of RP103 in adults and pediatric patients six years of age and older. The sponsor plans to study patients (b) (4) (4) (b) (4) A long-term safety study, RP103-04, is currently in progress (b) (4)

2.6.1.2 What pregnancy and lactation use information is there in the application?

No new studies were conducted to address pregnancy or lactation. (b) (4)

2.6.2 Does genetic variation impact exposure and/or response?

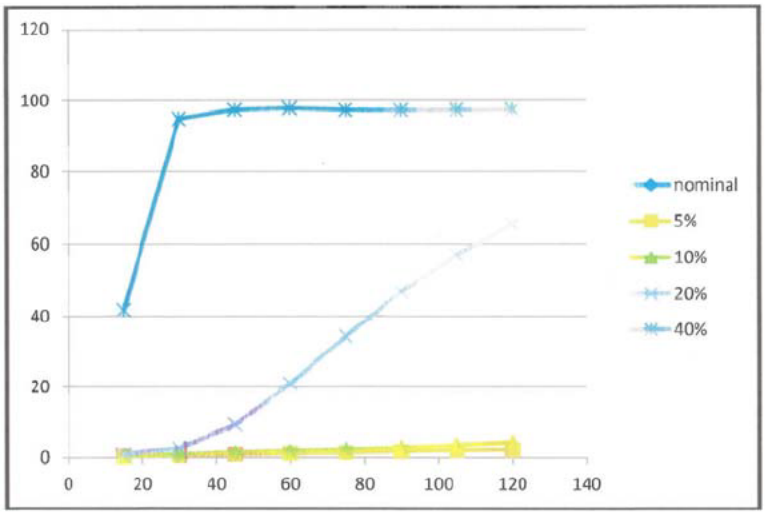
The impact of genetic polymorphisms on systemic exposure and pharmacodynamic response were not explored.

## 2.7 Extrinsic Factors

2.7.1 What extrinsic factors influence exposure or response and what is the impact of any differences in exposure on pharmacodynamics?

The impact of extrinsic factors such as drugs, herbal products, diet, smoking, and alcohol use on the PK or PD of RP103 in healthy volunteers or patients were not explored in this submission. However, the sponsor did conduct one in vitro study to assess the impact of ethanol on dose dumping.

Figure 5. Acid phase f2 comparison plot of drug release in varying ethanol concentrations




The test was performed using the 75 mg RP103 drug product in ethanol concentrations ranging from 0 to 40% for up to one hour. Samples exposed to 5 or 10% ethanol did not demonstrate dose dumping; however, samples exposed to 20 and 40% ethanol did demonstrate an increase in the release of cysteamine in acidic conditions. The ONDQA reviewer recommends labeling language stating that (b) (4) This recommendation appears reasonable based on the data.

2.7.2 Drug-Drug Interactions

2.7.2.1 Is the drug a substrate of CYP enzymes?

A study was performed to evaluate the metabolic stability of cysteamine bitartrate in pooled human liver microsomes (HLM) in the presence and absence of NADPH. Cysteamine bitartrate was incubated with pooled HLM in a phosphate buffer for up to 60 minutes. Following 60 minutes of incubation, the percent of cysteamine remaining was 68.3% in the presence of NADPH and 88% in the absence of NADPH. The results of this study showed little metabolism by liver microsomes. See 2.5.4.

2.7.2.2 Is the drug an inhibitor and/or an inducer of CYP enzymes?

*CYP Inhibition*

The inhibition IC50 values of cysteamine bitartrate for cytochrome P450 (CYP) enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) in human liver microsomes (HLM) were measured. The test compound at eight concentration levels (0-100 µM) was incubated with pooled HLM (0.25 mg protein/mL) in phosphate buffer (100 mM, pH 7.4) containing MgCl2 (5 mM), CYP-specific probe substrate (at approximately Km), and NADPH (1 mM). CYP enzyme activity was measured by determining the formation of the CYP probe metabolite by LC/MS/MS, and the IC50 was estimated by a non-linear regression analysis.

Table 12. Cysteamine bitartrate $IC_{50}$ of CYP enzymes in HLM

| CYP | % Enzyme Activity of Control (n=2)[a] | | | | | | | | $IC_{50}$ (µM) |
|---|---|---|---|---|---|---|---|---|---|
| | 0 µM | 0.137 µM | 0.412 µM | 1.23 µM | 3.70 µM | 11.1 µM | 33.3 µM | 100 µM | |
| CYP1A2 | 100 | 113 | 116 | 108 | 128 | 120 | 116 | 119 | >100 |
| CYP2A6 | 100 | 108 | 108 | 104 | 108 | 111 | 122 | 116 | >100 |
| CYP2B6 | 100 | 105 | 109 | 117 | 110 | 99.1 | 91.3 | 85.7 | >100 |
| CYP2C8 | 100 | 90.0 | 94.5 | 92.7 | 98.3 | 101 | 93.12 | 95.9 | >100 |
| CYP2C9 | 100 | 110 | 112 | 108 | 105 | 108 | 123 | 109 | >100 |
| CYP2C19 | 100 | 107 | 105 | 105 | 108 | 115 | 109 | 109 | >100 |
| CYP2D6 | 100 | 116 | 120 | 121 | 117 | 111 | 108 | 103 | >100 |
| CYP2E1 | 100 | 114 | 108 | 104 | 114 | 96.2 | 80.5 | 74.6 | >100 |
| CYP3A4 (Testosterone) | 100 | 123 | 107 | 119 | 121 | 121 | 128 | 144 | >100 |
| CYP3A4 (Midazolam) | 100 | 100 | 95.8 | 96.5 | 101 | 97.9 | 104 | 104 | >100 |

a Percent enzyme activity of control = 100 x (Enzyme activity in the presence of test compound / Enzyme activity in the absence of test compound). Enzyme activity was calculated based on the peak area ratio of the CYP probe metabolite to the internal standard by LC-MS/MS. Data were expressed as the average of duplicate experiments.

The inhibition $IC_{50}$ values of cysteamine bitartrate for all tested CYP enzymes were greater than 100 µM. This value is 10-fold higher than the mean $C_{max}$ observed in patients indicating a low potential for systemic drug interactions. The concentration of cysteamine bitartrate at the level of the gut (mean dose / 250 mL) is approximately 36.8 mM, which greatly exceeds the $IC_{50}$ (> 360-fold) described in this in vitro study; however, this is likely an overestimate given the actual value exceeds 100 uM. The clinical implications of this finding are not clear. All positive controls performed in parallel showed acceptable inhibition $IC_{50}$ values (data not shown), indicating that the HLM used in this study were metabolically active.

*CYP Induction*

With regard to enzyme activity, cysteamine bitartrate did not cause induction of CYP1A2, CYP2B6, or CYP3A4 at any tested concentration. However, mRNA levels were observed to increase in several donor systems following incubation with cysteamine bitartrate. The results were not consistent between donors and the sponsor did not determine a cutoff value to define an inducer.

Table 13. Induction of CYP1A2 mRNA by cysteamine bitartrate

| Donor | Compound | Treatment | $2^{-\Delta\Delta Ct}$ (mean, n=3) | SD | Normalized $2^{-\Delta\Delta Ct}$ | Fold-Induction[a] |
|---|---|---|---|---|---|---|
| 1 | Control | Solvent | 1.00 | 0.07 | 0.77 | 1.0 |
| | | BNF | 5.25 | 0.28 | 3.69 | 4.8 |
| | Cysteamine Bitartrate | 7 µM | 2.15 | 0.04 | 1.63 | 2.1 |
| | | 70 µM | 2.91 | 0.26 | 2.01 | 2.6 |
| | | 700 µM | 5.28 | 0.05 | 3.73 | 4.8 |
| 2 | Control | Solvent | 1.00 | 0.07 | 1.41 | 1.0 |
| | | BNF | 56.4 | 0.28 | 50.5 | 36 |
| | Cysteamine Bitartrate | 7 µM | 7.18 | 0.04 | 6.51 | 4.6 |
| | | 70 µM | 11.8 | 1.10 | 10.9 | 7.7 |
| | | 700 µM | 6.44 | 0.05 | 6.33 | 4.5 |
| 3 | Control | Solvent | 1.00 | 0.08 | 2.65 | 1.0 |
| | | BNF | 9.24 | 0.32 | 25.5 | 10 |
| | Cysteamine Bitartrate | 7 µM | 1.27 | 0.03 | 3.43 | 1.3 |
| | | 70 µM | 1.25 | 0.08 | 3.56 | 1.3 |
| | | 700 µM | 1.42 | 0.11 | 4.13 | 1.6 |

a Fold-induction was calculated based on the normalized mRNA level ($2^{-\Delta\Delta Ct}$) of the test compound or the positive control relative to that of the vehicle control.

CYP1A2 mRNA level increased in hepatocyte donor 1 at 700 µM (4.8-fold) and in hepatocyte donor 2 at 7 (4.6-fold), 70 (7.7-fold), and 700 (4.5-fold) µM.

Table 14. Induction of CYP2B6 mRNA by cysteamine bitartrate

| Donor | Compound | Treatment | $2^{-\Delta\Delta Ct}$ (mean, n=3) | SD | Normalized $2^{-\Delta\Delta Ct}$ | Fold-Induction[a] |
|---|---|---|---|---|---|---|
| 1 | Control | Solvent | 1.00 | 0.01 | 0.65 | 1.0 |
| | | PB | 3.26 | 0.02 | 2.04 | 3.1 |
| | Cysteamine Bitartrate | 7 µM | 2.68 | 0.04 | 1.76 | 2.7 |
| | | 70 µM | 0.46 | 0.03 | 0.31 | 0.5 |
| | | 700 µM | 3.96 | 0.16 | 2.33 | 3.6 |
| 2 | Control | Solvent | 1.00 | 0.09 | 1.56 | 1.0 |
| | | PB | 29.8 | 2.33 | 30.4 | 20 |
| | Cysteamine Bitartrate | 7 µM | 1.19 | 0.03 | 0.98 | 0.63 |
| | | 70 µM | 2.03 | 0.27 | 1.49 | 1.0 |
| | | 700 µM | 9.37 | 0.92 | 7.33 | 4.7 |
| 3 | Control | Solvent | 1.00 | 0.00 | 2.70 | 1.0 |
| | | PB | 13.1 | 0.13 | 33.0 | 12 |
| | Cysteamine Bitartrate | 7 µM | 1.39 | 0.06 | 3.70 | 1.4 |
| | | 70 µM | 1.79 | 0.07 | 4.76 | 1.8 |
| | | 700 µM | 2.33 | 0.34 | 6.67 | 2.5 |

a Fold-induction was calculated based on the normalized mRNA level ($2^{-\Delta\Delta Ct}$) of the test compound or the positive control relative to that of the vehicle control.

Cysteamine bitartrate demonstrated greater than 4-fold induction of CYP2B6 mRNA level in hepatocyte donor 2 at 700 µM (4.7-fold).

Table 15. Induction of CYP3A4 mRNA by cysteamine bitartrate

| Donor | Compound | Treatment | $2^{-\Delta\Delta Ct}$ (mean, n=3) | SD | Normalized $2^{-\Delta\Delta Ct}$ | Fold-Induction[a] |
|---|---|---|---|---|---|---|
| 1 | Control | Solvent | 1.00 | 0.10 | 0.68 | 1.0 |
| | | RIF | 75.4 | 3.32 | 51.2 | 75 |
| | Cysteamine Bitartrate | 7 µM | 1.68 | 0.03 | 1.16 | 1.7 |
| | | 70 µM | 2.45 | 0.10 | 1.61 | 2.4 |
| | | 700 µM | 1.15 | 0.11 | 0.95 | 1.4 |
| 2 | Control | Solvent | 1.01 | 0.14 | 1.08 | 1.0 |
| | | RIF | 209 | 4.11 | 223 | 207 |
| | Cysteamine Bitartrate | 7 µM | 3.69 | 0.38 | 3.52 | 3.3 |
| | | 70 µM | 6.89 | 0.33 | 6.23 | 5.8 |
| | | 700 µM | 5.92 | 0.50 | 7.52 | 7.0 |
| 3 | Control | Solvent | 1.01 | 0.13 | 2.81 | 1.0 |
| | | RIF | 136 | 9.94 | 371 | 132 |
| | Cysteamine Bitartrate | 7 µM | 4.71 | 0.52 | 12.9 | 4.6 |
| | | 70 µM | 14.8 | 0.35 | 35.9 | 13 |
| | | 700 µM | 1.86 | 0.25 | 5.08 | 1.8 |

a Fold-induction was calculated based on the normalized mRNA level ($2^{-\Delta\Delta Ct}$) of the test compound or the positive control relative to that of the vehicle control.

For CYP3A4 mRNA, cysteamine bitartrate showed greater than 4-fold induction in hepatocyte donor 2 at 70 (5.8-fold) and 700 (7.0-fold) µM and in hepatocyte donor 3 at 7 (4.6-fold) and 70 (13-fold) µM.

The results of the induction study using mRNA are not consistent between donor hepatocytes and, in the absence of a predetermined cutoff value, no conclusion may be drawn regarding the potential of cysteamine bitartrate to induce CYP enzymes 1A2, 2B6, or 3A4.

2.7.2.3 Is the drug a substrate and/or an inhibitor of P-glycoprotein (or other) transporters?

*Transporter affinity*

Caco-2 cells and CPT-P1 cells were used to determine the substrate/inhibition properties of cysteamine bitartrate toward P-gp and BCRP. Evaluation of cysteamine bitartrate as a substrate of efflux transporters was carried out at concentrations of 7.8, 78 and 780 µM in Caco-2 cells. In addition, the bidirectional permeability of cysteamine bitartrate was assessed in the presence of CsA and Ko143. Cysteamine bitartrate did not demonstrate inhibition towards P-gp or BCRP at the tested concentration (1000 µM), and the results indicated that cysteamine bitartrate is not an inhibitor of either P-gp or BCRP. Cysteamine bitartrate exhibited efflux ratios of 3.6, 4.3, and 0.55 at the concentrations of 7.8, 78, and 780 µM in the absence of inhibitors. In the presence of cyclosporine (a P-gp and BCRP inhibitor) and Ko143 (a BCRP inhibitor), its efflux ratio was 2.5 and 4.3, respectively; the percentage inhibition was 54.5% and approximately 1% in the presence of cyclosporine and Ko143. The results suggest that cysteamine is a P-gp substrate but not a BCRP substrate and cysteamine is not an inhibitor of either transporter.

An additional in vitro study was conducted in transfected HEK cells to assess if cysteamine was a substrate or inhibitor of the following uptake transporters: OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2. Cysteamine bitartrate (up to 780 µM) caused no inhibition of atorvastatin uptake in OATP1B1-HEK cells and OATP1B3-HEK cells; no inhibition of *p*-aminohippurate uptake in OAT1-HEK cells; no inhibition of furosemide uptake in OAT3-HEK cells; 41.4% and 32.0% inhibition of methylphenylpyridinium iodide in OCT1-HEK cells and OCT2-HEK cells, respectively. The 780 µM concentration of cysteamine bitartrate tested in these inhibition studies is approximately 10 times the mean steady state plasma $C_{max}$ observed in clinical studies at therapeutic doses. The inhibition did not exceed 50%; therefore, cysteamine bitartrate is not classified as an inhibitor of any of these six uptake transporters. In OATP1B1-, OATP1B3-, OAT1-,

OAT3, or OCT1-transfected HEK cells, cysteamine bitartrate (up to 78 µM) uptake was nearly identical to that in vector control cells; therefore, cysteamine bitartrate is not categorized as a substrate for these transporters. In the OCT2-transfected cells, the uptake ratio was greater than 2.0 and this uptake was completely inhibited by the presence of imipramine. The results indicate that cysteamine bitartrate is an OCT2 substrate.

2.7.2.4 What other co-medications are likely to be administered to the target patient population?

Electrolyte and mineral replacements may be used for the management of Fanconi Syndrome as well as vitamin D and thyroid hormone.

2.7.2.5 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No, in vivo drug-drug interactions studies were not performed with RP103. It may be reasonable to include the results of the CYP induction study in the label in lieu of additional clinical drug interaction studies.

2.7.2.6 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No, there is no known mechanism for a PD interaction.

2.7.2.7 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

The sponsor has not provided data to indicate whether cysteamine bitartrate has any active metabolites or to detail the potential for protein binding. However, given the availability of an important biomarker to assess response, these parameters are not required to be well characterized in order to adequately treat cystinosis patients.

2.7.3 What issues related to dose, dosing regimens, or administration are unresolved, and represent significant omissions?

There does not appear to be any significant omissions with regard to dose, regimen, or administration in the current application.

## 2.8 General Biopharmaceutics

2.8.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The product used in the clinical trial is the same as the TBM product.

2.8.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on plasma cysteamine exposure was explored in two studies (RP103-01, and -05); however, study -01 included usable data from only four subjects. The finding of a significant food effect for RP103 in study -01 was unexpected and the blood sampling scheme was not able to adequately capture the profile.

*Study RP103-05*

This was a single-center, open-label, randomized, 3-period study to evaluate the bioequivalence of 2 different modes of administration of RP103 following a 600 mg dose in healthy subjects under fasted conditions. The third period was included in this study to

address the effect of food on RP103. See Section 2.5.1 for a detailed description of the first two periods of the study.

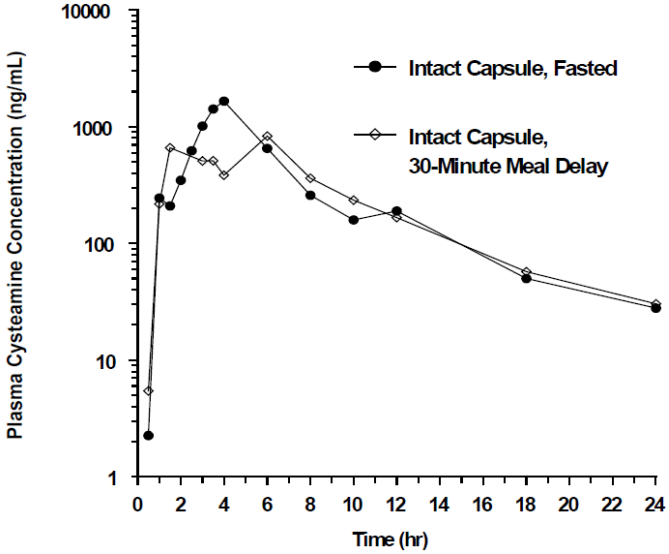
Seventeen subjects participated in the food effect portion of the study. Period 3 dosing was conducted using the same opened and intact capsule dosing procedures described for Periods 1 and 2 with the exception of the post-dose fasting interval. These groups were studied in parallel so subjects were randomized to only one treatment. Subjects were randomized to 1 of 4 capsule treatment/meal delay schedules:

AM1: Treatment A (Opened Capsules); Meal 1 (30 minutes post-dose)
AM2: Treatment A (Opened Capsules); Meal 2 (2 hours post-dose)
BM1: Treatment B (Intact Capsules); Meal 1 (30 minutes post-dose)
BM2: Treatment B (Intact Capsules); Meal 2 (2 hours post-dose)

A standardized breakfast that contained approximately 500 calories made up of 88% carbohydrate, 6% protein and 6% fat 2 hours was administered 30 minutes or 2 hours after dosing. It should be noted that this standard meal does not align closely with the high-fat meal advocated by the Agency to address the worst-case scenario with regard to food effect.

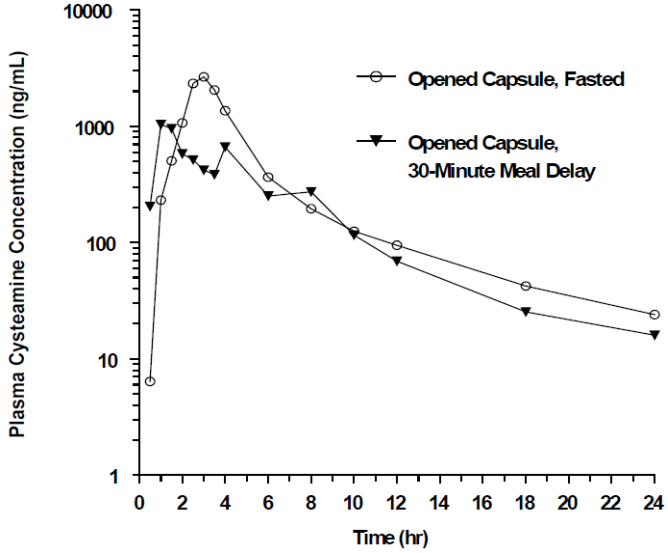
Subjects who participated in Period 3 had previously enrolled in the first two periods in which RP103 was administered as an intact capsule or sprinkled over applesauce. Therefore, the PK profile in each subject following administration of RP103 30 minutes or 2 hours prior to a 500 calorie meal can be compared to earlier PK profiles under fasted conditions.

Figure 6. Mean plasma cysteamine concentration-time profiles in 5 healthy subjects administered as a single 600 mg dose of RP103 intact capsules 30 minutes after a meal or in the fasted state.



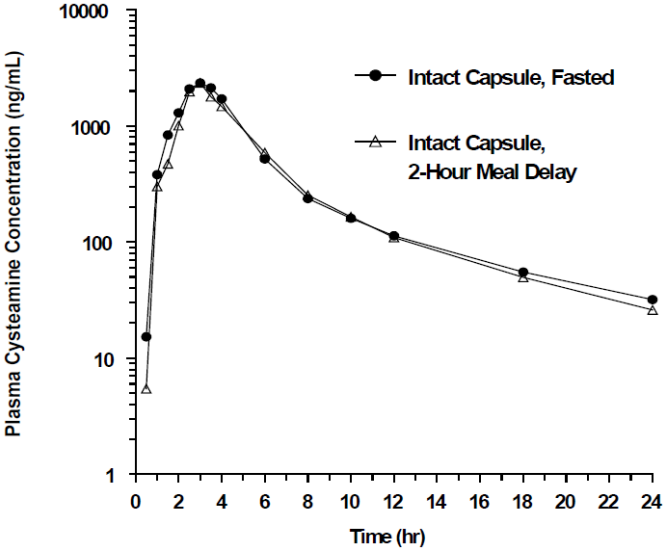

Geometric mean cysteamine $C_{max}$ and AUC are reduced by 23% and 18%, respectively, in subjects who received RP103 intact capsules 30 minutes following a 500 calorie meal relative to those administered the drug in the fasted state. There also appears to be two peaks, including an early peak between 1 and 2 hours, in the group receiving the meal 30 minutes post-dose.

Figure 7. Mean plasma cysteamine concentration-time profiles in 2 healthy subjects administered as a single 600 mg dose of RP103 opened capsules 30 minutes after a meal or in the fasted state.



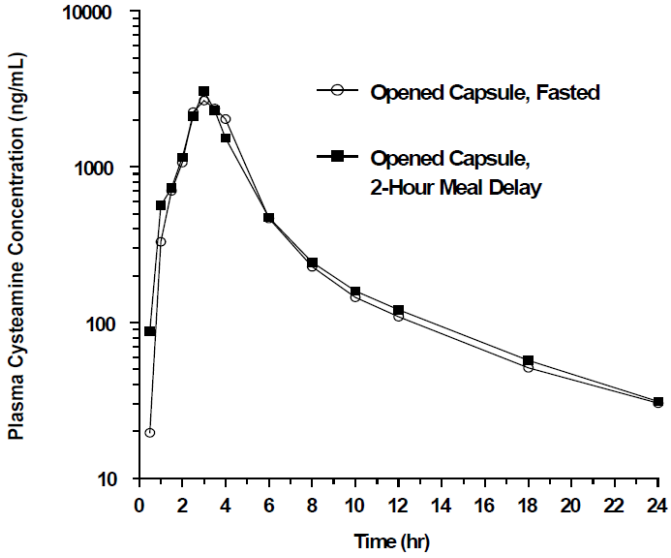

Geometric mean cysteamine $C_{max}$ and AUC are reduced by 45% and 31%, respectively, in subjects who received RP103 opened capsules 30 minutes following a 500 calorie meal relative to those administered the drug in the fasted state. This difference appears to be greater than the apparent difference in Figure 6 above, in which subjects received the *intact* capsule 30 minutes prior to a meal; however, the number of subjects with data available from administration of the opened capsule in the fasting and fed states was very small (n=2). There also appears to be an early peak at approximately 1 hour and there may be a late peak as well in the group receiving the meal 30 minutes post-dose. Given the reduction in exposure and the change in $t_{max}$ following the 30 minute meal-delay in the opened capsule group, there is the potential to have a clinically meaningful difference in response that should be reflected in the label.

Figure 8. Mean plasma cysteamine concentration-time profiles in 5 healthy subjects administered as a single 600 mg dose of RP103 intact capsules 2 hours after a meal or in the fasted state.



There was no reduction in mean plasma cysteamine exposure in subjects who received RP103 intact capsules 2 hours following a 500 calorie meal relative to those administered the drug in the fasted state.

Figure 9. Mean plasma cysteamine concentration-time profiles in 4 healthy subjects administered as a single 600 mg dose of RP103 opened capsules 2 hours after a meal or in the fasted state.




There was no reduction in mean plasma cysteamine exposure in subjects who received RP103 opened capsules 2 hours following a 500 calorie meal relative to those administered the drug in the fasted state.

Overall, the results show that a meal consumed 2 hours post-dose had little to no effect on the bioavailability or cysteamine bitartrate. However, a meal consumed 30 minutes post-dose appeared to reduce overall exposure, especially in the opened capsule group, and caused either a significantly shorter or longer $t_{max}$ relative to administration in the fasted state. The number of subjects used in several subgroups of this study were small, making a definitive determination of the impact of a small meal following drug administration difficult to determine. The conduct of these studies differs from the pivotal trial (study -03) in which patients were provided with a small meal or snack 30 minutes *prior* to study drug administration on clinic days. Although a direct comparison of the data is difficult due to the different populations and RP103 dose administered, the median $t_{max}$ in patients in study -03 who were administered a small meal 30 minutes prior to dosing is similar to the $t_{max}$ in healthy adults who received RP103 two hours prior to a small meal.

Given the importance of maintaining WBC cystine below a defined threshold value and the potential for a change in PK parameters depending on how the drug is administered, it may be reasonable to recommend patients take the drug in a consistent manner; patients should consistently administer RP103 with a small meal (or approximately the same time pre-dose or post-dose) or administer consistently in the fasted state (our hour before or two hours after meals). As the product is titrated to response and based on tolerance, the impact of food on cysteamine exposure would not be important if administered consistently.

In addition to the food effect studies, several food/liquid compatibility studies were performed to support labeling in the dosage and administration section of the label. The CMC review by Dr. Jane Chang describes the conduct of stability studies with orange

juice, apple juice, 7Up® (degassed), Fanta® (degassed, orange), Gatorade® (degassed, orange), PolyCitra, tap water (pH ~ 5.5) apple sauce, peanut butter (smooth), strawberry yogurt (held at room temperature and 5ºC), orange sherbet (held at room temperature until started to melt, ~ 20 minutes), and berry jelly. She concluded that a maximum hold time of 30 minutes for liquids (pH < 5.5) and two hours for the foods including apple sauce, peanut butter, yogurt, and berry jelly. The mixture of beads and yogurt may be stored at room temperature or at 5ºC.

The sponsor also performed a study to determine the ability to administer capsule contents through a feeding tube. Beads were administered in tap water and in applesauce. The CMC reviewer concluded that administration of beads swirled in tap water resulted in settling of the beads; however, administration with applesauce at a slow rate (1 mL/sec) was successful.

## 2.9 Analytical Section

2.9.1 How are active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The sponsor used LC/MS/MS to determine both plasma cysteamine concentrations and WBC cystine content.

2.9.2 Which metabolites have been selected for analysis?

No metabolites were analyzed in the PK studies.

2.9.3 What bioanalytical methods are used to assess concentrations? What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The sponsor used LC/MS/MS to determine both plasma cysteamine concentrations and WBC cystine content.

*WBC Cystine*
In general, cystine was quantitated from human WBC lysate by mixing the supernatant obtained after centrifugation with isotope-labeled cystine as an internal standard. The mixture was injected into an LC-MS/MS system using a SIELC Primesep 200 column with an ammonium formate/ acetonitrile mobile phase. This method was validated for a range of 4.00- 1500 ng/mL (Cystine). Two sets of standard calibrators were included in each analytical batch, one set placed at the beginning and one at the end. Calibration curves for each run were obtained by using a $1/concentration^2$ weighted least squares linear regression of peak area ratio versus concentration. The range of the standard curve was 4.00- 1500 ng/mL.

Total protein content in human WBC) lysate was measured using the bicinchoninic acid assay. The final step of sample collection at the clinical facility was acidification to precipitate the proteins. To analyze the samples for total protein the samples were centrifuged to obtain a protein pellet, the supernatant decanted and retained, then 0.1N NaOH is added to the pellet to dissolve the proteins. The total protein concentration was indicated by a color change of the sample solution from green to purple in proportion to protein concentration, which was quantitated with reference to bovine serum albumin calibrators by monitoring the absorbance at 562 nm.

*Plasma Cysteamine*
Cysteamine was extracted from sodium heparinized human plasma by a protein precipitation extraction with acetonitrile. Before the extraction, isotope-labeled drug was added as an internal standard, and Tris(2-carboxyethyl)phosphine hydrochloride was added as a reducing agent. A supernatant was transferred to a new plate, and diluted with mobile phase. The sample was injected into an LC-MS/MS system using a Waters

HILIC column with an ammonium formate / acetonitrile / water mobile phase. The range of the standard curve was 75 - 10,000 ng/mL and was appropriate for the clinical trials.

2.9.3.1 What are the lower and upper limits of quantification (LLOQ/ ULOQ) and what are the accuracy, precision and selectivity at these limits? What is the QC sample plan?

*WBC Cystine*

Human WBC lysate was spiked with solutions of cystine and total protein to achieve nominal analyte concentrations in the range 4.00- 1500 ng/mL (cystine) and 25.0 - 2000 µg/mL (total protein). For quality control, human WBC lysate was spiked with solutions of cystine and total protein to achieve nominal analyte concentrations of 12.0, 600, 1200 ng/mL (cystine), 75.0, 800, and 1600 µg/mL (total protein). The acceptance criteria were met for all calibration standards and QC samples.

*Plasma Cysteamine*

For quantification of cysteamine, QC plasma samples were spiked with solutions of cysteamine to achieve concentrations of 75.0, 200, 4,000, and 7,500 ng/mL. The accuracy at these concentrations ranged from -7.6 to 2.3 and the precision was ≤ 6.4 in all runs.

2.9.3.2 What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

*Plasma cysteamine*
To determine the sample stability, sets of QC samples initially frozen for at least 24 hours at -20±10°C and -80 ± 20°C were allowed to thaw at room temperature. The samples were then refrozen for at least 12 hours before beginning another cycle. Stability was evaluated through 5 cycles. The samples were assayed against a freshly prepared calibration curve. The 5 cycle freeze/thaw stability data meet the precision and accuracy criteria. At ambient conditions, the samples were stable for approximately 24 hours.

3 Detailed Labeling Recommendations

The sponsor has proposed to include recommendations regarding the use of (b) (4) with RP103 despite the absence of any in vivo studies to support the recommendations. The Agency recommends deleting references to a drug interaction with (b) (4) until a clinical study can be conducted to elucidate the effect on the cysteamine PK profile. The sponsor also makes reference to suitable soft foods that may be used to administer RP103 to patients unable to swallow the intact capsule. Studies were conducted using applesauce and orange juice but the inclusion of additional products would require submission of stability data. Given the results of in vitro studies indicating that cysteamine may be an inducer of specific SYP enzymes, it may be appropriate to include this information in the label despite the lack of clinical studies.

The clinical pharmacology section of the proposed label includes a significant amount of information regarding the (b) (4) which is not necessary for RP103, other than to describe important differences between the two products.

# 4 Appendices

## 4.1 Consult Reviews

Pharmacometrics Review
Inspection Report

# OFFICE OF CLINICAL PHARMACOLOGY:
# PHARMACOMETRIC REVIEW

## 1 SUMMARY OF FINDINGS

### 1.1 Key Review Questions

The purpose of this review is to address the following key questions.

#### 1.1.1 Do the results of the dose-response analysis support the sponsor's proposed dosing regimen?

No. The reviewer's analysis finds three points to suggest that the starting dose of RP103 should contain the same amount of cysteamine as the patients maintenance Cystagon® dose:

1. The dose-response analysis (Figure 1) suggests that patients who switched to a lower dose of cysteamine bitartrate (70 to 80% of prior Cystagon® dose) with RP103 administration as compared to Cystagon administration had reduced benefit in lowering the concentrations of white-blood-cell (WBC) cystine.
2. The clinical trial data indicate that patients doses were generally increased throughout the trial and a protocol amendment was submitted to increase the RP103 dose patients were to initially receive.
3. Finally, the original proposed label doses and dose amounts administered during the trial were incorrectly determined. After correct analysis of the dosage forms it is apparent that the Cystagon dosage forms contained 85% of the stated dose and the RP103 contained ~91% of the stated dose in the phase III clinical trial. This would suggest that the amounts of cysteamine administered with RP103 are closer to that with Cystagon than initially anticipated. See the CMC review by Dr. Jane Chang for further details. The corrected dose amounts are used in the reviewer's analysis.

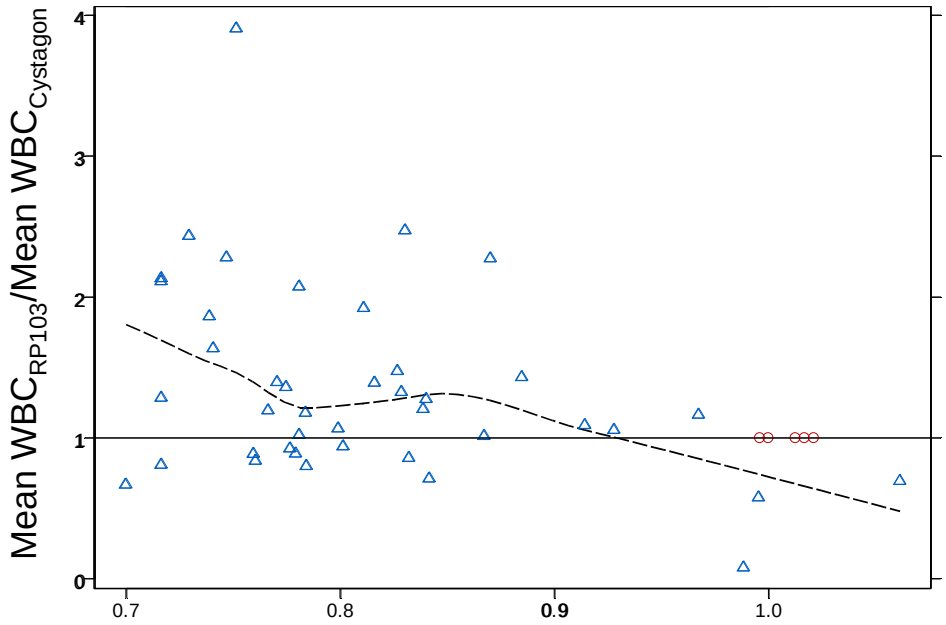
Furthermore, there are no serious safety signals that suggest the dose needs to be reduced for RP103.

Study RP103-03 was an open-label randomized two period crossover design to compare the reduction in WBC cystine at the end of three weeks of treatment between RP103 and Cystagon. The y-axis of Figure 1 shows the ratio of the WBC cystine concentrations at the end of the three week period (average of three visits) following RP103 relative to Cystagon. The higher the value, the less effect RP103 has in reducing WBC cystine compared to Cystagon. The x-axis shows the Time-averaged dose relative to the Cystagon run-in dose during screening. Patients must have been on a prior stable dose of Cystagon before being enrolled and randomized in the trial. At the start of the trial patients were to receive 70% of the Cystagon dose with RP103 administration. The protocol was later amended to increase the dose of cysteamine bitartrate received with their initial administration of RP103 (80% of prior Cystagon dose).

Because of the crossover design, dose-response could be used to evaluate the appropriate dose conversion as CL and body-surface area are the same between the compared treatment periods for each individual. In other words, because the analysis was a comparison between doses and

responses within each individual and the product is being approved for switching from a prior dose of Cystagon, covariates that explain inter-patient variation (CL, BSA, etc.) were not necessary to determine the starting dose for this analysis.

**Figure 1. Relative WBC Cystine after RP103 to WBC Cystine after Cystagon is higher in patients with reduced total cysteamine bitartrate in the dosage form. Each point represents data for one individual. Blue triangles indicate results from patients receiving RP103. Red circles indicate results from patients receiving Cystagon.**




Additionally the following summary statistics of the doses in study RP103 suggest that increasing the proposed starting dose (to be the same as the Cystagon dose) is consistent with the dose adjustments made in study RP103-03.

For the population who completed the trial (n=41):

- Ratio of RP103 End Dose to RP103 Start Dose: median = 1.17 (95% CI = 1, 1.27)
- Ratio of RP103 Start Dose to Cystagon Run-In Dose: median = 0.76 (95% CI = 0.72, 1.0)
- Ratio of RP103 End Dose to Cystagon Run-In Dose: median = 0.91 (95% CI = 0.72, 1.0)

### 1.1.2 What % of dose amount should be used for the titration?

The dose amount should be increased 25% as a starting point to improve efficacy. This is the dose increase amount recommended by the agency based on preliminary phase I data (see the agencies response to Raptor's specific protocol assessment in DARRTS, March 2010 by PeiFan Bai, PhD) and is the average increase in dose for patients who required dose increase in the phase III trial (see the following paragraph). In brief, in the agencies SPA response, clinical trial simulation results indicated that the sponsor's proposed 10% increase in dose would likely not be sufficient to elicit a drop of 0.3 nmol ½ cystine/mg protein of white-blood cell cystine in every individual. Using the sponsor's PK/PD relationship and PK information the clinical trial

simulation results indicated that dose increases of 25% should be sufficient for improving efficacy.

Using dosing and WBC cystine data from study RP103-03, the amount of dose increase was evaluated for patients who had dose increases between the start and finish of RP103 therapy. Out of 41 patients who completed, 23 had their dose increased. The results (below) suggest that for these patients a 25% increase in RP103 dose was sufficient to achieve WBC cystine concentrations below 1.0 nmol ½ cystine/mg protein (the desired level to maintain WBC cystine concentrations below).

For the population who had dose increase:

- Ratio of RP103 End Dose to RP103 Start Dose (median=1.24, 95% CI=1.10,1.28)
- Ratio of RP103 Start Dose to Cystagon Run-In Dose (median=0.76, 95% CI=0.72,0.91)
- Ratio of RP103 End Dose to Cystagon Run-In Dose (median=0.94, 95% CI=0.90,1.05)

### 1.1.3 Are the studied doses and proposed dose amounts consistent with prior approved doses?

Yes. The proposed Cystagon dose for treatment naive patients less than 12 years and 110 pounds is 1300 mg/m$^2$/day the proposed dose for 12 or older and 110 pounds or older is 2000 mg/m$^2$/day. The following median doses from the run-in and crossover periods do not exceed these previously approved/labeled Cystagon doses.

- Median Baseline Run in Cystagon dose is 1343 (95% CI=896, 1850) mg/m$^2$/day
- Median Time-Averaged Cystagon Dose is 1343 (95% CI=896, 1850) mg/m$^2$/day
- Median Time Averaged RP103 Dose 1072 (95% CI=707, 1500) mg/m$^2$/day

The above summary statistics are shown by age and age and body weight criteria in Table 1. Three points should be noted from this table:

1. The studied doses dose amounts do not exceed the prior approved doses for Cystagon.
2. RP103 doses were increased by their last dose regardless of age or body weight.
3. Cystagon run-in and time-averaged doses and RP103 time-averaged doses do not appear to require a dose increase with age or body weight, as approved previously for Cystagon.

**Table 1. Summary of doses administered (mg/m$^2$/day) in Study RP103-03 indicates studied daily doses do not exceed previous approved doses for Cystagon. Results are presented as median (95% CI).**

| Dose Metric/ Demographic | Age < 12 | Age ≥ 12 | BW < 110 | BW ≥ 110 | Age < 12 &/OR BW < 110 | Age ≥ 12 and BW ≥ 110 |
|---|---|---|---|---|---|---|
| **Baseline Run-In Cystagon** | 1418 (921, 1770) | 1244 (811, 1890) | 1356 (864, 1870) | 1216 (1040, 1500) | 1356 (864, 1870) | 1216 (1040, 1500) |
| **Time-Averaged Cystagon** | 1418 (933, 1770) | 1244 (811, 1890) | 1356 (864, 1870) | 1214 (1060, 1500) | 1356 (864, 1870) | 1214 (1060, 1500) |
| **Time-Averaged RP103** | 1107 (851, 1480) | 952 (590, 1630) | 1100 (676, 1540) | 953 (861, 1170) | 1100 (676, 1540) | 953 (861, 1170) |
| **Ending RP103** | 1167 (898, 1670) | 1101 (265, 1720) | 1148 (441, 1770) | 1084 (917, 1370) | 1148 (441, 1770) | 1084 (917, 1370) |

This leads us to the conclusion that the labeled dosing recommendations for RP103 should not be defined by age or body weight.

Time-averaged dose is the time-weighted average of the doses and includes doses that were insufficient to maintain WBC cystine concentrations below 1.0 nmol ½ cystine/mg protein. Doses at the end of the 3-week treatment period reflect a better measure of the patients necessary RP103 dose (see Sections 1.1.1 and 1.1.2)

### 1.2 Recommendations

The Office of Clinical Pharmacology, Division of Pharmacometrics has reviewed this application and found it to be approvable. We recommend the sponsor:

- Match the total daily dose of cystagon that patients are on when switched to RP103 instead of reducing the amount of drug received to ensure better reduction of white-blood-cell cystine concentrations.
- When increasing the dose, adjust the dose amount by 25%. The proposed labeling does not indicate how much to increase or decrease the dose based on efficacy.

### 1.3 Label Statements

Labeling recommendations are made on page 26.

## 2 PERTINENT REGULATORY BACKGROUND

Raptor is submitting a 505(b)(2) New Drug Application (NDA) for cysteamine bitartrate delayed-release capsules (RP103) for the management of nephropathic cystinosis in children and adults. The reference drug and the basis for the application is Cystagon®, NDA 20-392. Cystagon was approved for use as a four times daily administration on August 15, 1994. Raptor is seeking approval for a twice daily administration of cysteamine bitartrate.

In the current submission the efficacy results of the pivotal phase III trial indicate non-inferiority to Cystagon with regards to reduction in white-blood-cell cystine levels after 3 weeks of therapy in an open-label, randomized, crossover trial.

## 3 RESULTS OF SPONSOR'S ANALYSIS

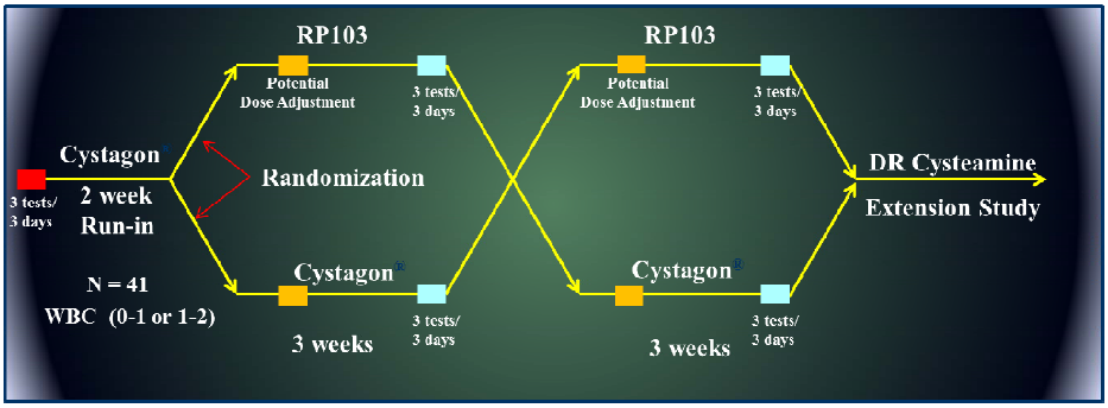
### 3.1 Clinical Trials

Data for the reviewer's analysis came from the phase III study RP103-03 and its ongoing 2-year extension study, RP103-04. The sponsor's PK/PD model was generated with data from study RP103-03.

#### 3.1.1 Trial RP103 – 03

This was a phase III, open-label, randomized crossover, PK and PD study to determine the safety and efficacy of RP103 compared to Cystagon in subjects with nephropathic cystinosis. Subjects were eligible if they were on a stable dose of Cystagon, considered sufficient to maintain their white blood cell cysteine level at ≤2.0 nmol ½ cystine/mg protein. The study schematic is shown in Figure 2 and consists of a 2-week run-in phase followed by two 3-week periods.

**Figure 2. Schematic of the Phase III trial design (RP103-03)**




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

The primary endpoint was to demonstrate that comparable depletion of steady-state cysteamine-trough white-blood-cell cystine levels is achieved following treatment with either Cystagon or RP103. The pre-specified analysis was a one-sided, non-inferiority test, conducted at the nominal level of 0.02104 with a non-inferiority margin of 0.3 (overall significance level of 0.025). RP103 was determined to be non-inferior to Cystagon within the margin of 0.3. Forty-three subjects were enrolled and randomized and 41 subjects completed the study.

### 3.1.2 Trial RP103 – 04

This is an ongoing long-term, open-label, safety and efficacy study of cysteamine bitartrate delayed-release capsules (RP103) in patients with cystinosis. Subjects in RP103-03 who completed the last visit were offered the opportunity to enroll in this extension study. Subjects who did not participate in RP103-03 are also enrolled in RP103-04. The study is planned to enroll approximately 60 individuals (40 subjects continued from RP103-03). The primary objective of this study is to evaluate the long-term safety and efficacy of RP103. Efficacy is assessed by white-blood-cell cystine concentrations.

Data from this trial are reviewed in Section 4.4.1 to evaluate whether the sponsor's proposed dosing regimen is consistent with the doses patients were titrated to in study RP103-04.

## 3.2 Population PK of RP103

The sponsor conducted separate structural population PK analyses for the phase III study in patients with nephropathic cystanosis and in two bioequivalence trials in healthy volunteers. These models were developed using Phoenix software (Certera, ) using non-linear mixed effects modeling. However, potential intrinsic factors such as body weight, age, gender, race, etc were not assessed as covariates on the model parameters. The sponsor evaluated the effects of dose and food using data from the bioequivalence studies. No parameters were added for food effect rather the parameter estimates were compared between studies. These results are outlined in Section 2.5.1. In brief, the structural model is a 2-compartment linear PK model with first order absorption and lag-time in absorption.

*Reviewer's Comments: The sponsor's population PK analysis only evaluated the structural PK model and did not assess the effect of demographics or extrinsic factors as covariates on RP103 PK. Conducting separate analyses for each study limited the number of subjects in each analysis*

*to between 6 and 38. The fact that the dose is titrated for each individual's response and that there are no major safety concerns, suggests that a covariate analysis of factors affecting inter-patient variability is not absolutely necessary for RP103 dosing recommendations.*

### 3.3 Population PK/PD Model

A population PK/PD model combining the 2-compartment PK model to an inhibitory $E_{max}$ PD model was fitted to characterize the pharmacodynamics of WBC cystine. The sponsor did not fix the PK parameters as part of this evaluation, but rather re-estimated them along with the pharmacodynamic parameters. This led to slightly different estimates from the parameters obtained by fitting only the cysteamine PK. Parameter estimates for the sponsor's PK/PD model are shown in Table 2.

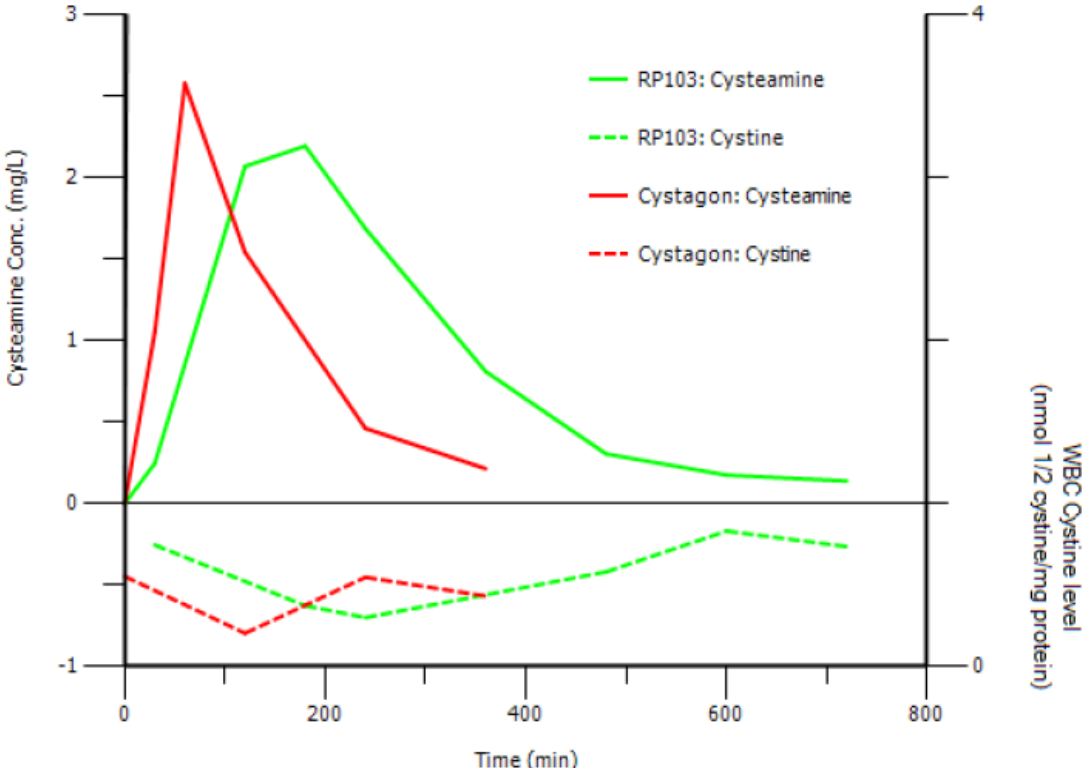
**Table 2. 2-compartment population PK and Inhibitory $E_{max}$ PD parameters in patients after a single, variable dose of Cystagon® or RP103 at steady state.**

| | $T_{lag}$ (min) | $K_a$ (1/min) | V/F (L) | Cl/F (L/min) | $V_2$ (L) | $Cl_2$ (L/min) |
|---|---|---|---|---|---|---|
| Cystagon® | 27.8 ± 1.1 | 0.099 ± 0.039 | 109 ± 8 | 1.03 ± 0.07 | 184 ± 57 | 0.42 ± 0.06 |
| RP103 | 57.5 ± 0.4 | 0.013 ± 0.001 | 68 ± 10 | 0.97 ± 0.01 | 296 ± 49 | 0.38 ± 0.01 |

| | $IC_{50}$ (mg/L) | $E_0$ (nmol ½ cystine/mg protein) |
|---|---|---|
| Cystagon® | 1.69 ± 0.44 | 0.46 ± 0.05 |
| RP103 | 0.72 ± 0.01 | 0.70 ± 0.01 |

*(Source: Sponsor's Population PK/PD Report, Table 9)*

**Figure 3. Average cysteamine concentration and average WBC cystine level as predicted by a 2-compartment population PK model and inhibitory $E_{max}$ PD model in patients after a single, variable dose of Cystagon® or RP103 at steady-state.**




*(Source: Sponsor's Population PK/PD Report, Figure 8)*

*Reviewer's Comments: The sponsor's use of a direct effect $E_{max}$ model (no lag between PK and PD) is acceptable given the time course of response relative the PK concentrations (i.e. peak effect is observed at the same time as peak concentrations). The utility of the model for dosing recommendations is limited however, in that it only captures the population trend and does not evaluate covariate effects or the amount of increase in dose required to elicit a meaningful change in WBC cystine concentrations.*

# 4 REVIEWER'S ANALYSIS

## 4.1 Introduction

While the sponsor's PK/PD analysis establishes a correlation between concentration and response, it does not address the question of whether the dose was selected optimally. The reviewer's analysis aims to identify if response after Procysbi administration is different that after Cystagon administration and if trends exist what the Procysbi dose should be.

## 4.2 Objectives

Analysis objectives are:

1. To determine whether the dose of cysteamine bitartrate was selected appropriately for Procysbi

## 4.3 Methods

### 4.3.1 Data Sets

Data sets used are summarized in Table 3.

**Table 3. Analysis Data Sets**

| Study Number | Name | Link to EDR |
|---|---|---|
| RP103-03 | adex.xpt | \\cdsesub1\EVSPROD\NDA203389\0000\m5\datasets\rp103-03\analysis\adam\datasets |
| RP103-03 | adpd.xpt | \\cdsesub1\EVSPROD\NDA203389\0000\m5\datasets\rp103-03\analysis\adam\datasets |
| RP103-04 | adpdc.xpt | \\cdsesub1\EVSPROD\NDA203389\0000\m5\datasets\rp103-03\analysis\adam\datasets |

### 4.3.2 Software

The statistical software S-plus (Tibco, Palo Alto, CA) was used to generate all plots.

### 4.3.3 Models

No original models were developed as part of this review.

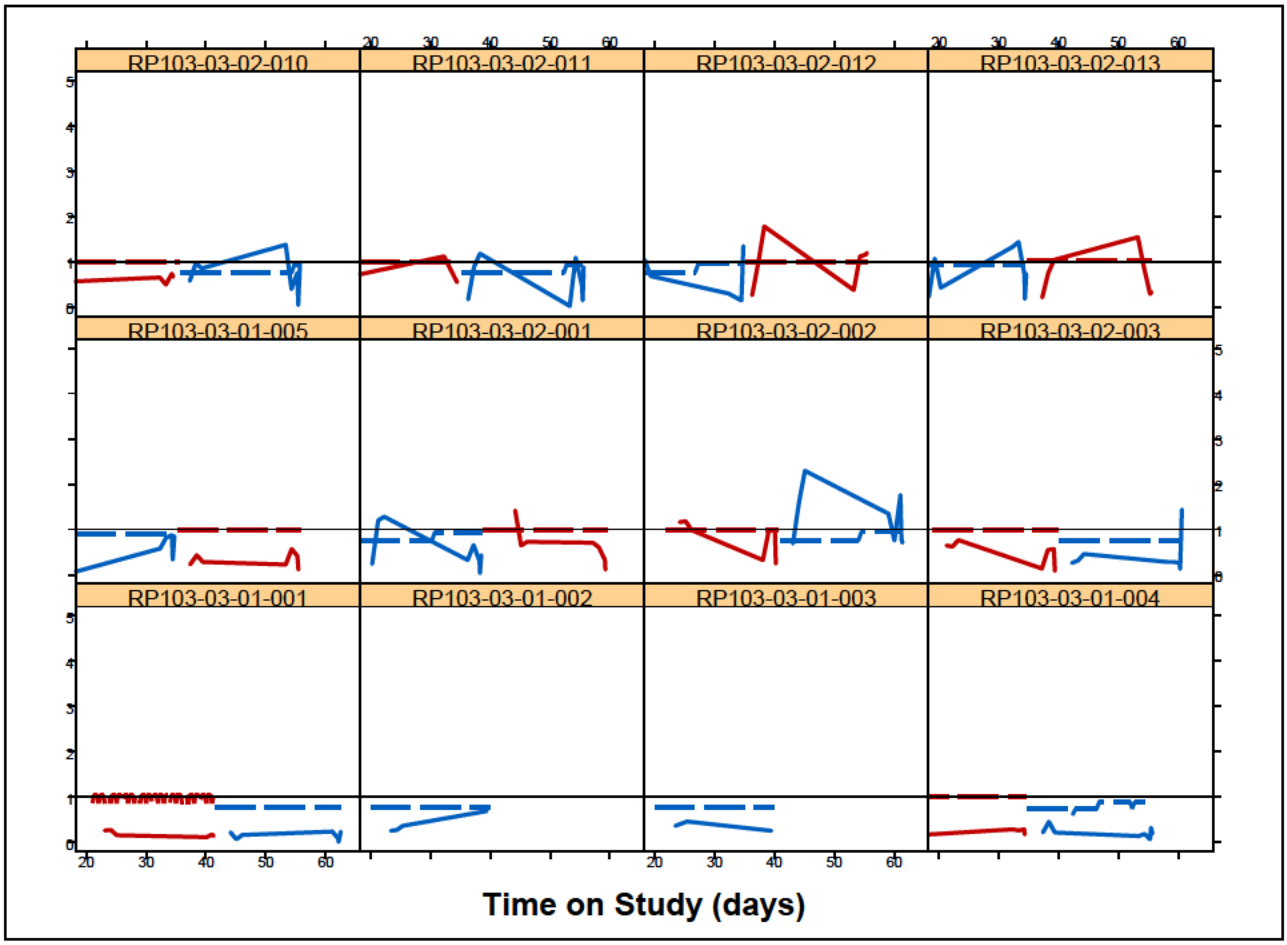
## 4.4 Results

### 4.4.1 Conversion Dose from Cystagon to RP103

The reviewer's primary analysis results are shown in Section 1.

The following two figures (Figure 4 and Figure 5) are additional results in support of the FDA recommendation of dosing RP103 the same amount as the prior the total daily Cystagon dose or Cystagon starting maintenance dose, instead of the sponsor's proposal to administer 70% of the prior Cystagon daily dose when switching to RP103. Figure 4 shows the time course of response and dose for each individual. This figure was used as an initial assessment of dose response and it is apparent in some individuals that when the total cysteamine bitartrate dose is decreased, the reduction in WBC cystine is reduced (higher WBC cystine concentrations). Figure 5 indicates that the WBC cystine response after RP103 is numerically less than after administration of Cystagon.

**Figure 4. Time Courses of Dose Relative to Cystagon-Run-in Dose (dashed lines) and WBC Cystine Concentrations (nmol ½ cystine/mg protein, solid lines) for Each Patient in Study RP103-03. Red and blue lines indicate Cystagon and RP103 treatments, respectively. Data from the screening and run-in stages of the trial are not shown.**



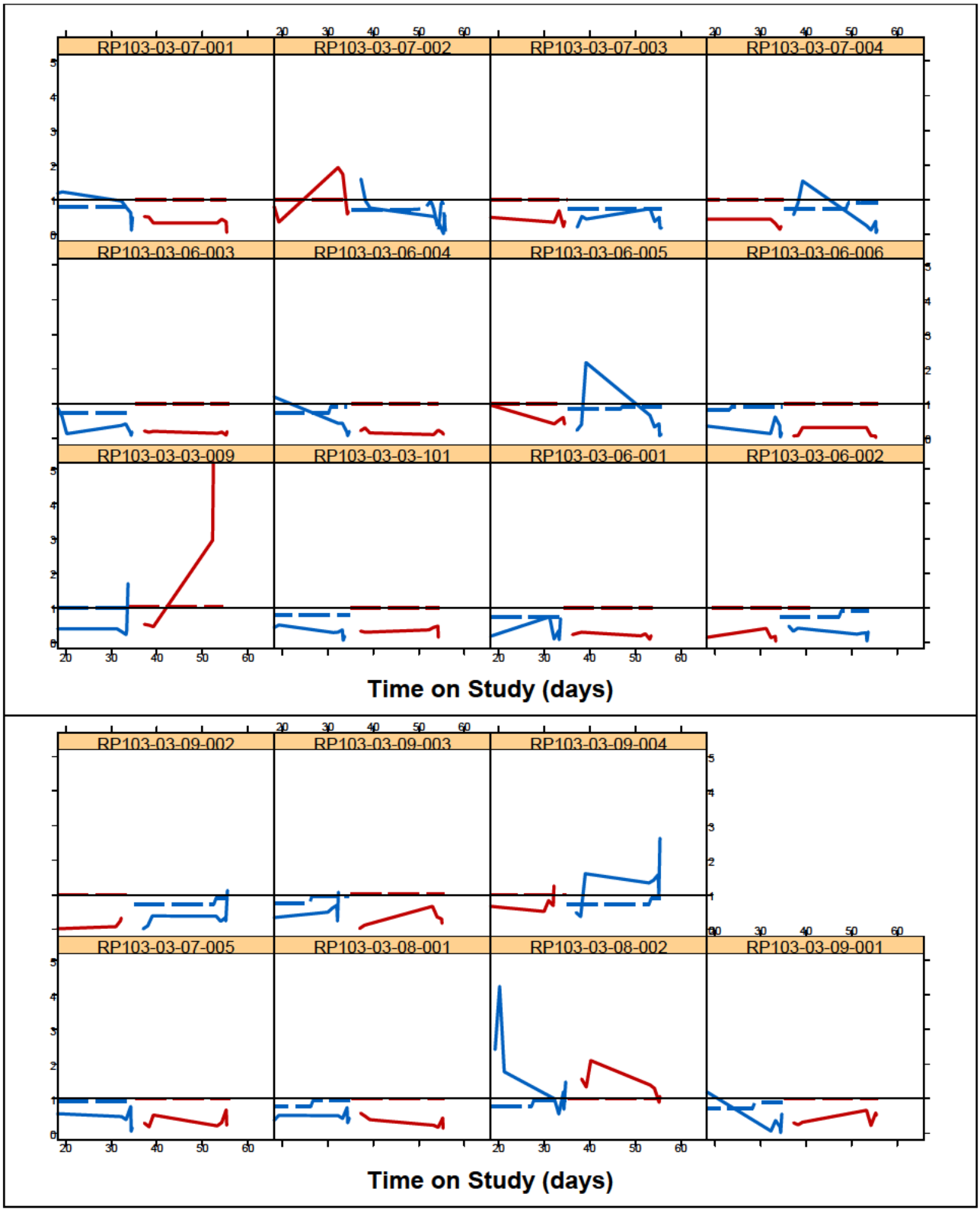
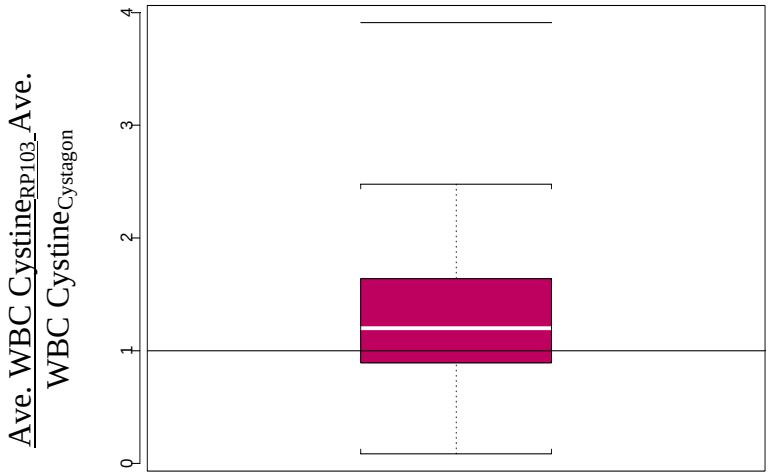


**Figure 5. Response after RP103 Administration is Less than After Cystagon Administration in Study RP103-03. Results are shown as the ration of the average WBC cystine concentrations at the end of each 3-week treatment period.**




Dosing data from the ongoing extension trial were evaluated to determine if the patient's RP103 dose was titrated further after completion of the RP103-03 study. For patients in Study RP103-04, the mean ending dose was 1.01-fold that of the starting dose of RP103. There was not a signficant difference between the starting and ending doses in this trial, suggesting that the 3 week period to titrate doses in Study RP103-03 was sufficient to reach a maintenance dose.

### 4.4.2 Starting Dose for Treatment Naive Patients

The sponsor's proposed labeling indicates a starting dose for patients not receiving Cystagon, even though this population was not studied. If approved for treatment naive subjects, the recommended starting maintenance dose is the same recommended starting dose as for Cystagon (1.3 g/m$^2$/day for patients (b) (4) This is because the reviewer's analysis recommends switching from Cystagon to RP103 with the same amount of cysteamine. Further, the median doses in the older group in Study RP103-03 were not higher than those for the younger group on a mg/m$^2$ basis. Thus, it appears reasonable that all patients could start at 1.3 g/m$^2$/day of RP103 instead of breaking the dose by age and bodyweight. Study RP103-03 dosing was not done by age and body weight.

# 5 LISTING OF ANALYSES CODES AND OUTPUT FILES

| File Name | Description | Location in \\cdsnas\pharmacometrics\ |
|---|---|---|
| PKPD.ssc | Dose-Repsonse Analysis for Original Datasets | \PM Review Archive\2013\Cysteamine_Bitartrate_NDA203389_JCE\ ER Analyses |
| PKPDreviseddata.ssc | Dose-Repsonse Analysis for Revised Dosing Information | \PM Review Archive\2013\Cysteamine_Bitartrate_NDA203389_JCE\ ER Analyses |

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KRISTINA E ESTES
04/03/2013

JUSTIN C EARP
04/04/2013

NITIN MEHROTRA
04/04/2013

SUE CHIH H LEE
04/04/2013

| BIOPHARMACEUTICS REVIEW<br>Office of New Drug Quality Assessment | | | |
|---|---|---|---|
| **Application No.:** | NDA 203-389 | **Reviewer:** Kareen Riviere, Ph.D. | |
| **Submission Date:** | 3/30/2012; 5/29/2012; 07/18/2012; 10/16/2012; 11/1/2012; 12/14/2012; 2/13/2013 | | |
| **Division:** | DGIEP | **Acting Team Leader:** Tapash Ghosh, Ph.D. | |
| **Sponsor:** | Raptor Therapeutics, Inc. | **Acting Supervisor:** Richard Lostritto, Ph.D. | |
| **Trade Name:** | Procysbi | **Date Assigned:** | 4/30/2012 |
| **Generic Name:** | Cysteamine Bitartrate | **Date of Review:** | 2/14/2013 |
| **Indication:** | Treatment of nephropathic cystinosis in children and adults | **Type of Submission:** 505(b)(2) New Drug Application | |
| **Formulation/strengths:** | DR capsules/ 25 mg and 75 mg | | |
| **Route of Administration:** | Oral (whole capsule; sprinkles on food or in liquid) | | |


**SUMMARY:**

This submission is a 505(b)(2) New Drug Application for a delayed release capsule formulation containing 25 mg and 75 mg of cysteamine bitartrate. The proposed indication is for the treatment of nephropathic cystinosis in children and adults. The reference drug is Cystagon (NDA 20-392), which is an immediate release tablet.

The Biopharmaceutics information in the orginial submission included a drug product development section with the proposed dissolution method and the proposed acceptance criteria in the acid and buffer stage.

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criteria as well as the in vitro alcohol dose-dumping information that was requested.


**A. Dissolution Method**

The proposed two-stage dissolution method is shown below.

**Acidic Buffer Stage**

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| I | 75 rpm | 1000 mL | 37°C | 0.1 N HCl |

**Basic Buffer Stage**

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| I | 75 rpm | 1000 mL | 37°C | 0.2 M sodium phosphate buffer pH 6.8 |

The proposed dissolution method has adequate discriminating power and, therefore, is deemed acceptable.

**B. Acceptance Criteria**

The proposed dissolution acceptance criteria are shown below.

| Acceptance Criterion in Acidic Buffer |
|---|
| Q = NMT (b) (4) at 2 hours |

| Acceptance Criterion in Basic Buffer |
|---|
| (b) (4) |

The proposed dissolution acceptance criterion for the basic buffer stage is considered too permissive. In an IR letter to the Applicant dated February 12, 2013, the ONDQA Biopharmaceutics team recommended a dissolution acceptance criterion of Q = (b) (4) at 20 minutes for the basic buffer stage based on the mean *in vitro* dissolution profiles of the clinical and registration batches at release and stability. In a submission dated February 13, 2013, the Applicant accepted the Agency's recommendation.

**C. *In Vitro* Alcohol Interaction Study**

An IR letter was sent to the Applicant on May 18, 2012 requesting that they conduct and *in vitro* alcohol dose dumping study. Data provided in the amendment submitted on July 18, 2012 demonstrate that the proposed drug product exhibits alcohol induced dose dumping *in vitro* in 0.1N HCl containing 20% and 40% alcohol. This reviewer communicated to the Clinical and Clinical Pharmacology review teams about this issue in an email dated July 24, 2012.

**D. Information to Support Approval of Lower Strength**

The Applicant conducted one pivotal Phase 3 study with the 25 mg and 75 mg strengths, (b) (4) Therefore, a biowaiver is not required for the approval of the 25 mg strength.

**RECOMMENDATION:**

1. Procysbi (cysteamine bitartrate) 25 mg and 75 mg strength delayed release capsules are recommended for approval from a Biopharmaceutics standpoint with the following dissolution method and acceptance criteria for both strengths.
    i. Acidic Buffer Stage Dissolution Method: Apparatus I, 75 rpm agitation rate, 1000 mL media volume, 37 °C, 0.1 N HCl buffer.
    ii. Basic Buffer Stage Dissolution Method: Apparatus I, 75 rpm agitation rate, 1000 mL media volume, 37 °C, 0.2 M sodium phosphate buffer pH 6.8.
    iii. Dissolution acceptance criterion for Acidic Buffer Stage: NMT (b) (4) at 2 hours.
    iv. Dissolution acceptance criterion for Basic Buffer Stage: Q = (b) (4) at 20 minutes.

**Kareen Riviere, Ph.D.**
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

**Tapash Ghosh, Ph.D.**
Biopharmaceutics Team Leader (acting)
Office of New Drug Quality Assessment

cc: Dr. Angelica Dorantes, Dr. Richard Lostritto

# ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

## 1. Background

### Drug Substance

Figure 1 displays the structure of cysteamine bitartrate.

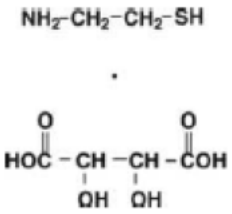


**Figure 1.** Chemical structure of cysteamine bitartrate

The Applicant stated that cysteamine bitartrate has a solubility of >100 mg/mL in water. They did not provide the solubility in aqueous buffer.

### Drug Product

The proposed drug product is an enteric-coated microbead formulation. The composition is displayed in Table 1.

**Table 1.** Composition of Cysteamine Bitartrate DR Capsules

| Raw Material | Purpose | Grade | Amount (mg) / 75 mg Capsule | Amount (mg)/ 25 mg Capsule |
|---|---|---|---|---|
| Cysteamine bitartrate | Active ingredient | (b) (4) | 221.10 (equivalent to 75 mg of cysteamine free base) | 73.70 (equivalent to 25 mg of cysteamine free base) |
| Microcrystalline Cellulose (b) (4) (b) (4) | | | | (b) (4) |
| Hypromellose (b) (4) | | | | |
| Sodium lauryl sulfate | | | | |
| Eudragit L30D55 | | | | |
| Triethyl citrate | | | | |
| Talc | | | | |
| Purified water | | | | |
| Hard gelatin capsule, size 0 – 75 mg strength (refer to Table 2) | | | | |
| Hard gelatin capsule, size 3 – 25 mg strength (refer to Table 3) | | | | |
| White (b) (4) (refer to Table 4) | | | | |

***Reviewer's Assessment:***
***The 25 mg and 75 mg strengths of the proposed drug product are*** (b) (4)

## 2. Dissolution Method

The proposed two-stage dissolution method is shown below.

**Acidic Buffer Stage**

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| I | 75 rpm | 1000 mL | 37°C | 0.1 N HCl |

**Basic Buffer Stage**

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| I | 75 rpm | 1000 mL | 37°C | 0.2 M sodium phosphate buffer pH 6.8 |

In the original submission, there was limited information on the selection of the dissolution method parameters. Therefore, the following Biopharmaceutics comments were conveyed to the Applicant in an IR letter sent on May 18, 2012.

> **FDA Comment**
> There are insufficient data to support the adequacy of the selected dissolution method. Provide the dissolution method report supporting the selection of the proposed dissolution test. Include as part of the dissolution report the following information:
>
> a. A detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters supporting the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.). The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label claim or when a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.
>
> b. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method rejects batches that are not bioequivalent.

The Applicant provided additional data to support their proposed dissolution method in a submission dated May 29, 2012.

**Selection of the Dissolution Medium**

(b) (4)

**Reviewer's Figure 1 a and b.** Dissolution Profiles for 75 mg (b) (4) Capsules in Various Dissolution Media for Different Enteric Coating Levels (Basket, 75 rpm)

(b) (4)

The Applicant noted that when this study was performed, they had not established the practice of (b) (4)

The Applicant concluded that pH 6.8 is suitable (b) (4)

They did not evaluate pH levels between pH 6.0 and 6.8.

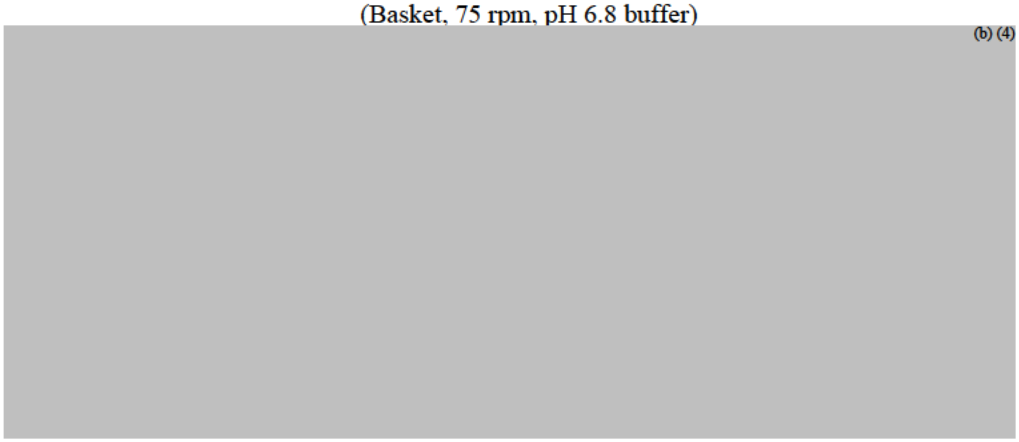
Note that the Applicant decided to develop and validate (b) (4)

**Evaluation of the Dissolution Method's Discriminating Ability**

(b) (4)

**Figure 2. Effect of Enteric Coating Level on Dissolution in Basic Buffer**
(Basket, 75 rpm, pH 6.8 buffer)

(b) (4)



***Reviewer's Assessment:***
***Reviewer's Figure 1 demonstrates that the proposed drug product*** (b) (4) ***Therefore, 0.1N HCl is acceptable as the acid stage dissolution medium. Figure 2 demonstrates that*** (b) (4) ***This reviewer calculated an f2 value of*** (b) (4) ***Therefore, pH 6.8 buffer is acceptable as the buffer stage dissolution medium.***

***The Applicant did not provide justification for their selection of the apparatus and agitation speed. However, Apparatus I (basket) is commonly used for capsule formulations. A 100 rpm agitation speed is a commonly used for Apparatus I. Therefore, the Applicant's selection of 75 rpm agitation could make the dissolution method more discriminating. However, there is no data to definitively conclude this. Nonetheless, as stated above, the proposed acid stage and buffer stage dissolution method is discriminating. Thus, the proposed apparatus and agitation speed are acceptable.***

***The Applicant proposed*** (b) (4) ***The Applicant must follow the USP dissolution method recommendation for delayed release formulations. Thus, the following Biopharmaceutics comment was conveyed to the Applicant in an IR letter sent on September 5, 2012.***

**FDA Comment**
The use of (b) (4) to evaluate the acid resistance and dissolution of your product is not acceptable. Conduct the acid resistance and dissolution testing on one set of capsules as described in the USP<711>, Delayed-Release Dosage Forms.

**Applicant's Response**
Test Method 929946, in compliance with USP<711>, has been validated. The test method and validation reported are provided in Sections 3.2.P.5.2 and 3.2.P.5.3, respectively. The method includes (b) (4)

***The Applicant followed the ONDQA Biopharmaceutics team's recommendation and has developed a two-stage dissolution method, which is acceptable.***

### 3. Dissolution Acceptance Criteria

The proposed dissolution acceptance criteria are shown below.

| Acceptance Criterion in Acid Buffer |
|---|
| Q = NMT (b) (4) at 2 hours |

| Acceptance Criterion in Basic Buffer |
|---|
| (b) (4) |

***Reviewer's Assessment:***
***The following Biopharmaceutics comment was conveyed to the Applicant in an IR letter sent on May 18, 2012.***

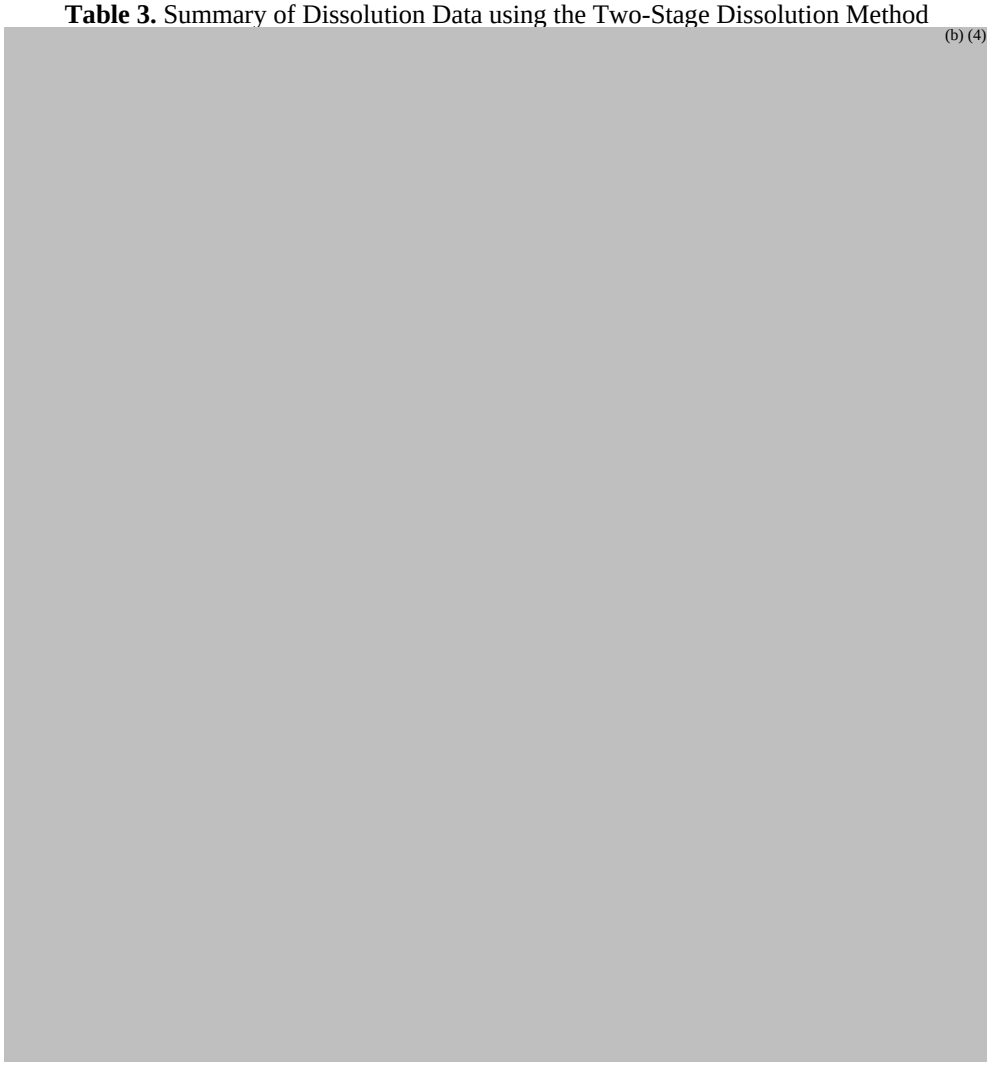
> **FDA Comment 2**
> Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for the proposed product.

***In a submission dated May 29, 2012, the Applicant provided stability data for the drug product*** (b) (4) ***which is against the USP recommendation for delayed release formulations. Thus, the following Biopharmaceutics comment was conveyed to the Applicant in an IR letter sent on September 5, 2012.***

> **FDA Comments**
> Revise the dissolution test for your delayed release product as per USP<711> and provide the complete dissolution profile data for the acid and buffer stages for the clinical batches of your proposed product (raw data and mean values). For the stability registration batches (remaining stability time points), conduct the dissolution profile testing and provide the data using both the proposed and the USP methods.
>
> Based on the data using the same set of capsules as per USP<711>, provide a proposal for the dissolution acceptance criteria (acidic and buffer stages) for your product.
>
> **Applicant's Response (excerpt)**
> Representative Rp103 drug product samples {lot release and stability, available at the time of analysis) were analyzed by the new 2 stage dissolution method 929946 to support a proposed acceptance criterion. Data are reported for the end of the acid stage (2 hours) and a (b) (4) buffer stahe dissolution profile (b) (4) These results as well as the results obtained during method validation and transfer to another laboratory are summarized.

The Applicant provided the requested data (refer to Table 3) in a submission dated December 14, 2012.

**Table 3.** Summary of Dissolution Data using the Two-Stage Dissolution Method




***Reviewer's Assessment:***

***Based on data in Table 3, the buffer stage criterion is too permissive and should be tightened to Q =*** (b) (4) ***at 20 minutes. The following Biopharmaceutics comment was conveyed to the Applicant in an IR letter sent on February 12, 2013.***

> **FDA Comment**
> Based on the mean *in-vitro* dissolution profiles for all strengths from clinical batches at release and under long term (18 months) stability, the following dissolution acceptance criterion for the buffer stage is recommended: Q = (b) (4) at 20 minutes. We recommend you to revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product by February 13, 2013.
>
> **Applicant Response**
> The Cysteamine Bitartrate Delayed-release Capsules (RP103) buffer stage dissolution acceptance criterion has been revised. The revised acceptance criterion for buffer stage dissolution is as follows: **Not less than** (b) (4) **(Q) of the label claim of cysteamine is dissolved in 20 minutes in sodium phosphate buffer, pH 6.8.**

***In a submission dated February 13, 2013, the Applicant accepted the ONDQA Biopharmaceutics team's recommendation to tighten the dissolution buffer stage acceptance criterion.***

## 4. Assessment of Alcohol Effect on *In Vitro* Drug Release

The original submission did not include an *in vitro* alcohol interaction study; therefore, the following Biopharmaceutics comment was conveyed to the Applicant in an IR letter sent on May 18, 2012.

**FDA Comment**

We are concerned that your delayed-release (DR) product may release its entire contents ("dose dumping") in the stomach when co-administered with alcohol. Therefore, we recommend that you evaluate the potential for a drug-alcohol interaction with your DR product using the following *in vitro* settings:

- Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed in 0.1 N HCl and in the proposed quality control medium. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
- The following alcohol concentrations for the *in vitro* dissolution studies are recommended: 0 %,5 %, 10 %, 20 %, and 40 %.
- The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
- The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
- The report with the complete data (i.e., individual, mean, standard deviation, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA within six weeks of the date of this letter.

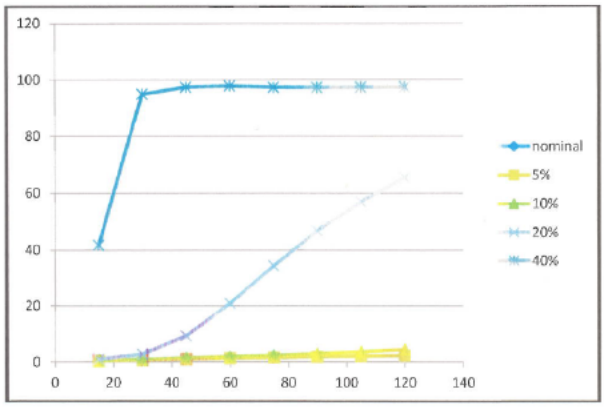
**Applicant's Response**

The report from the alcohol dose-dumping study is provided in Module 5.3.1.3. The results show samples exposed to 5% and 10% alcohol met the minimum acceptance criteria for acid phase and dissolution. Samples exposed to 20% and 40% did not meet the minimum acceptance criteria for acid phase and dissolution. Based on the results of the alcohol dose-dumping study, we conclude alcohol consumption should be limited while taking the drug. (b) (4)

(b) (4)

The Applicant provided the requested data in a submission dated July 18, 2012. The data is presented in Figures 3 and 4 as well as Reviewer's Tables 1and 2.

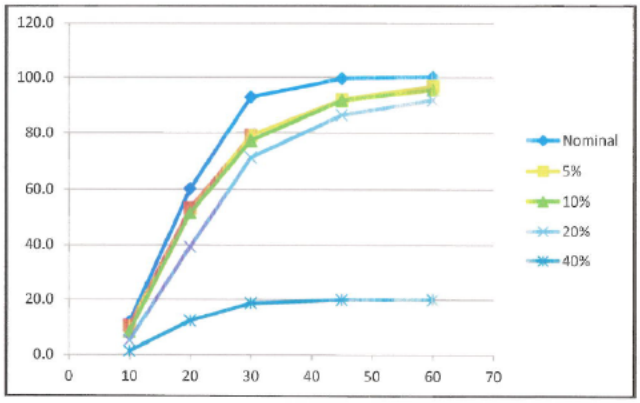
**Figure 3.** Dissolution Profiles of 75 mg (b) (4) Capsules in 0.1N HCl Containing Different Alcohol Concentrations



**Reviewer's Table 1**. f2 Similarity Factors for Drug Release in 0.1N HCl Media Containing Different Alcohol Concentrations (calculated by Applicant)

| Medium | f2 |
|---|---|
| 0% | - |
| 5% | 99.7 |
| 10% | 89.8 |
| 20% | 21.9 |
| 40% | 2.2 |

**Figure 4** Dissolution Profiles of 75 mg (b) (4) Capsules in pH 6.8 Buffer Containing Different Alcohol Concentrations




Note: The Applicant stated that the lack of complete drug release in the presence of 40% alcohol was due to the product forming large clumps on the dissolution basket.

**Reviewer's Table 2.** f2 Similarity Factors for Drug Release in pH 6.8 Buffer Containing Different Alcohol Concentrations (calculated by Applicant)

| Medium | f2 |
|---|---|
| 0% | - |
| 5% | 55.2 |
| 10% | 51.9 |
| 20% | 40.7 |
| 40% | 9.6 |

***Reviewer's Assessment:***

***The proposed drug product is not intended to release cysteamine bitartrate in an acidic pH environment. The data in Figure 3 demonstrate that greater than 60% of the total 75 mg strength is released within 2 hours in 0.1N HCl containing 20% alcohol, whereas greater than 90% of the total 75 mg strength is released within 20 minutes in 0.1N HCl containing 40% alcohol. Therefore, the proposed drug product exhibits alcohol induced dose dumping in vitro in 0.1N HCl containing 20% and 40% alcohol. This reviewer alerted the Clinical and Clinical Pharmacology review teams about this issue in an email dated July 24, 2012.***

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/s/

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KAREEN RIVIERE
02/14/2013

TAPASH K GHOSH
02/14/2013

# PRODUCT QUALITY - BIOPHARMACEUTICS
# FILING REVIEW

| | |
|---|---|
| **NDA Number** | 203-389 |
| **Submission Date** | 3/30/2012 |
| **Product name, generic name of the active** | Cysteamine Bitartrate |
| **Dosage form and strength** | DR capsules/ 25 mg and 75 mg |
| **Route of Administration** | Oral (whole capsule; sprinkles on food or in liquid) |
| **Indication** | Treatment of nephropathic cystinosis in children and adults |
| **Applicant** | Raptor Therapeutics, Inc. |
| **Clinical Division** | DGIEP |
| **Type of Submission** | 505(b)(2) |
| **Biopharmaceutics Reviewer** | Kareen Riviere, Ph.D. |
| **Acting Biopharmaceutics Lead** | Angelica Dorantes, Ph.D. |

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

| **ONDQA-BIOPHARMACEUTICS**<br>**A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING | | | | |
|---|---|---|---|---|
| | **Parameter** | **Yes** | **No** | **Comment** |
| 1. | Is the dissolution test part of the DP specifications? | x | | |
| 2. | Does the application contain the dissolution method development report? | | x | See Attachment. More information/data will be requested from the Applicant. |
| 3. | Is there a validation package for the analytical method and dissolution methodology? | x | | |
| 4. | Is there data from an *in vitro* alcohol interaction study? | | x | See Attachment. More information/data will be requested from the Applicant. |
| 5. | Does the application include a biowaiver request? | | x | Not applicable. Both strengths were tested in the single phase 3 study. |
| 6. | Does the application include a IVIVC model? | | x | Not applicable. |
| 7. | Is information such as BCS classification mentioned, and supportive data provided? | | x | |
| 8. | Is information on the effect of mixing the product with foods or liquids on the BA of the product included? | x | | BA/BE data were included to support the bioequivalence of whole capsules vs. capsule contents sprinkled on food. |
| 9. | Is there any in *vivo* BA or BE information in the submission? | x | | See response to Question 9. |
| 10. | Is information on the stability of the capsule contents sprinkled onto food products included? | | x | More information/data will be requested from the Applicant by the CMC reviewer. |

# PRODUCT QUALITY - BIOPHARMACEUTICS
# FILING REVIEW

| B. FILING CONCLUSION | | | | |
|---|---|---|---|---|
| | **Parameter** | **Yes** | **No** | **Comment** |
| 11. | **IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?** | x | | |
| 12. | If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant. | - | - | |
| 13. | Are there any **potential review** issues to be forwarded to the Applicant? | x | | IR comments will be sent to the Applicant prior to a filing action. The comments are outlined in the Attachment. |

*{See appended electronic signature page}*
Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

05/10/12
Date

*{See appended electronic signature page}*
Sandra Suarez-Sharp, Ph.D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

05/10/12
Date

# PRODUCT QUALITY - BIOPHARMACEUTICS
# FILING REVIEW

**ATTACHMENT**

**Biopharmaceutics Information:**

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method as well as the proposed acceptance criteria in the acid and buffer stage, and BA/BE data from three bioequivalence studies to support the bioequivalence of whole capsules vs. capsule contents sprinkled on food/liquid. The Applicant conducted only one pivotal phase 3 study with the 25 mg and 75 mg strengths. Therefore, a biowaiver is not required for the approval of the lower strength (25 mg).

The proposed dissolution method:

**Acid Stage**

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| I | 75 rpm | 1000 mL | 37°C | 0.1 N HCl |

**Buffer Stage**

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| I | 75 rpm | 1000 mL | 37°C | 0.2 M sodium phosphate buffer pH 6.8 |

The proposed dissolution acceptance criteria:

| Acid Stage Acceptance Criterion |
|---|
| Q = NMT (b) (4) at 2 hours |

| Buffer Stage Acceptance Criterion |
|---|
| (b) (4) |

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion as well as the in vitro alcohol dose-dumping information being requested.

To aid the review of the Applicant's submission, the following will be conveyed/requested:

1. There is insufficient data to support the adequacy of the selected dissolution method. (e.g. sink conditions, and dissolution apparatus are not justified). Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

    a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters supporting the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.). The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.

b. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.

2. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for all components of the proposed product.

3. We are concerned that your delayed release (DR) product may release its entire contents ("dose dumping") in the stomach when co-administered with alcohol defeating the purpose of the formulation. Therefore, we recommend that you evaluate the potential for a drug-alcohol interaction with your DR product in *in vitro* settings.
   - Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed in 0.1 N HCl and in the proposed QC medium. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
   - The following alcohol concentrations for the *in vitro* dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
   - The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
   - The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
   - The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA within six weeks of the expedition date of this letter.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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KAREEN RIVIERE
05/10/2012

SANDRA SUAREZ
05/10/2012