CLINICAL PROTOCOL

Protocol No.:	RP103-04
Title:	A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-release Capsules (RP103) in Patients with Cystinosis
Amendment 9:	**18 November 2015**
EudraCT No.:	2010-018365-34
Sponsor:	Raptor Pharmaceuticals Inc. 7 Hamilton Landing Suite 100 Novato, CA 94949 USA
Lead Investigator:	[redacted] Feinberg School of Medicine Northwestern University Ann & Robert H. Lurie Children's Hospital of Chicago 225 E. Chicago Avenue, #37 Chicago, IL 60611 USA

Clinical Development Approval:

[redacted]
Chief Medical Officer
Raptor Pharmaceuticals Inc.

[redacted] 11-18-15
Signature / Date

Investigator Agreement Page

Raptor Pharmaceuticals Inc.

RP103-04 Protocol Amendment 9
November 18, 2015

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the attached protocol, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all federal, state and local regulations, as well as with the requirements of the appropriate Institutional Review Board or Ethics Committee and any other local and institutional requirements.

_____ _____

Principal Investigator Signature **Date**

_____

Principal Investigator Full Name (please print)

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1. List of Abbreviations

Abbreviation or Term	Definition/Explanation
ADL	Activities of daily living
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase (Serum Glutamic Pyruvic Transaminase)
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AST (SGOT)	Aspartate aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
AOC	Area over the curve
AUC	Area under the curve
$AUC_{0\text{-}inf}$	Area under the curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the curve from time zero to time of the last quantifiable concentration
BCA	Bicinchoninic acid
BLQ	Below limit of quantification
BMI	Body mass index
BSA	Body surface area
C	Celsius
CFR	Code of Federal Regulations
CI	Confidence intervals
CIOMS	Council for International Organizations of Medical Sciences
C_{min}	Minimum concentration
C_{max}	Maximum concentration
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
EC	Ethics Committee
EC-Cystagon	Enteric-coated Cystagon® Capsules
ECG	Electrocardiogram
[redacted]	[redacted]
ESI	Electrospray ionization
FDA	Food and Drug Administration
G	Gram
HILC	Hydrophobic interaction liquid chromatography
HIPAA	Health Information Portability and Accountability Act of 1996
h	Hour
HPLC	High pressure liquid chromatography
ICF	Informed consent form
IND	Investigational new drug
IRB	Institutional Review Board
IUD	Intrauterine device
Kg	Kilogram
L	Liter

Abbreviation or Term	Definition/Explanation
LLOQ	Lower limit of quantification
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minute
mL	Milliliter
mmHg	Millimeters of mercury
MS	Mass spectrometry
OJ	Orange juice
OTC	Over the counter
Q6H	Every 6 hours
Q12H	Every 12 hours
QoL	Quality of Life
PD	Pharmacodynamic
PE	Physical examination
PI	Principal Investigator
PICC	Peripherally inserted central catheter
PK	Pharmacokinetic
PMNC	Polymorphonuclear and polynuclear granulocytes
PPD	Pharmaceutical Product Development, Inc.
RBC	Red blood cell
PVDS	Pharmacovigilance and Drug Safety
RP103	Cysteamine Bitartrate Delayed-release Capsules
SAE	Serious adverse event
SD	Standard deviation
SGOT (AST)	Serum glutamic oxaloacetic transaminase
SGPT (ALT)	Serum glutamic pyruvic transaminase
STV	Study termination visit
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal elimination phase half-life
T_{max}	Time to maximum concentration
UCSD	University of California San Diego
ULN	Upper limit of normal
[redacted]	[redacted]
WBC	White blood cell
WHO-DRL	World Health Organization-Drug Reference List

2. List of Tables and Figures

3. Study Synopsis

Protocol Title:	A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-release Capsules (RP103) in Patients with Cystinosis
Sponsor:	Raptor Pharmaceuticals Inc. 7 Hamilton Landing Suite 100 Novato, CA 94949 USA
Project Phase:	Phase IIIb
Indication:	Cystinosis (children and adults).
Objectives:	**Primary Objective:** • To assess safety and tolerability of long-term repeat dosing of RP103 in patients with cystinosis. **Secondary Objectives:** • To assess the steady-state pharmacokinetics (PK) and pharmacodynamics (PD) of RP103. • [redacted]
Study Design:	This is a long-term, open-label study of the safety, tolerability and steady-state pharmacokinetics and pharmacodynamics of RP103 in pediatric and adult patients with cystinosis. Patients who will have completed the last visit of the previous phase III Study (RP103-03) will be offered the opportunity to enroll in this extension Study. Additional patients, who did not complete the RP103-03 study, may be enrolled after completion of the analysis of the RP103-03 Study where the non-inferior efficacious and safe dose of RP103 versus Cystagon® has been determined. For patients who completed Study RP103-03, study visits will consist of: • Screening Visit which occurs simultaneously with the RP103-03 Period 2 Day 7 (End of Study) visit. • Monthly Study Visits which are only for patients who completed Study RP103-03 and begin within 1 month (± 7 days) after study entry. Each patient will complete a minimum of 6 consecutive Monthly visits. • Quarterly Study Visits which will commence for each patient ≥ 1 month and < 4 months after the patient has completed at least

	6 consecutive Monthly visits. Each Quarterly visit will take place by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15).
	
	For patients who did not complete Study RP103-03, study visits will consist of:
	
	• Screening Visit which may occur up to 28 days prior to Day 1.
	• Dose Confirmation Period (Days 1-5) which includes 3 study visits over 5 days.
	  • Day 1 includes a morning study visit while the patient is fasted, with pre-dose blood samples collected for trough cysteamine and peak WBC cystine determination while the subject is still taking Cystagon®. RP103 treatment regimen begins at the clinic on the morning of Day 1, administered Q12H at a starting total daily RP103 dose equal to 70% of the Screening total daily Cystagon® dose. Patients will leave the clinic for Days 2-3 and take RP103 as instructed.
	  • Days 4 and 5 each include a morning study visit; RP103 Q12H treatment regimen continues.
	• Quarterly Study Visits which will take place by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15).
	
	All patients, including those who did and those who did not complete Study RP103-03, will have an End of Study (EOS) Visit conducted within 7 (± 2 days) from the last completed study visit or from the date of decision to terminate.

Planned Sample Size:	Up to 60 patients may be enrolled. Initial sample size depends on the number of patients entering the Study from the RP103-03 Safety and Efficacy Study. Additional patients may be enrolled after all patients from Study RP103-03 have completed participation and results demonstrate non-inferiority of RP103 versus Cystagon® in reducing WBC cystine levels.
Total Number Of Centers:	Up to 10 sites in North America and Europe
Selection Criteria:	**Inclusion Criteria:** 1. Male and female subjects must have completed the last visit of Study RP103-03 and be willing to continue with RP103 treatment. OR for patients who did not complete the RP103-03 study:

	2. Male and female subject with a documented diagnosis of cystinosis. 3. Subject must be on a stable dose of Cystagon® at least 21 days prior to Screening. 4. [no longer applicable] 5. Within the last 6 months, no clinically significant change from normal in liver function tests [i.e., 1.5 times ULN for ALT and AST, and/or 1.5 times ULN for total bilirubin] and renal function [i.e., estimated GFR (corrected for body surface area)] at Screening as determined by the Investigator. 6. Subject must have an estimated GFR (corrected for body surface area) > 30 mL/minute/1.73 m^2. 7. Sexually active female subjects of childbearing potential (i.e., not surgically sterile [tubal ligation, hysterectomy, or bilateral oophorectomy] or at least 2 years naturally postmenopausal) must agree to utilize the same acceptable form of contraception from Screening through completion of the Study. The acceptable forms of contraception for this Study include hormonal contraceptives (oral, implant, transdermal patch, or injection) at a stable dose for at least 3 months prior to Screening, barrier (spermicidal condom, diaphragm with spermicide), IUD, or a partner who has been vasectomized for at least 6 months. For pre-pubescent children, a documented attestation of abstinence from their parent or guardian will be acceptable. 8. Subject must be willing and able to comply with the Study restrictions and requirements. 9. Subject or their parent or guardian must provide written informed consent and assent (where applicable) prior to participation in the Study. **Exclusion Criteria:** 1. Patients enrolled in the previous Study RP103-03 who did not complete their last scheduled study visit or who do not wish to continue on treatment with RP103. AND for patients who did not complete the RP103-03 study: 2. Subjects less than 1 year old. 3. Subjects with current history of the following conditions or any other health issues that make it, in the opinion of the Investigator, unsafe for them to participate: • Inflammatory bowel disease (if currently active) or prior resection of small intestine;

	• Heart disease (e.g., myocardial infarction, heart failure, unstable arrhythmias, or poorly controlled hypertension) 90 days prior to Screening; • Active bleeding disorder 90 days prior to Screening; • History of malignant disease within the last 2 years. 4. Subject with a hemoglobin level of < 10 g/dL at Screening or, in the opinion of the Investigator, a hemoglobin level that would make it unsafe for the subject to participate. 5. [no longer applicable] 6. Subjects with known hypersensitivity to cysteamine and penicillamine. 7. Female subjects who are nursing, planning a pregnancy, known or suspected to be pregnant, or with a positive serum pregnancy screen. 8. Subjects who, in the opinion of the Investigator, are not able or willing to comply with the protocol.
Study Drugs:	RP103: Cysteamine Bitartrate Delayed-release Capsules (75 mg and 25 mg of cysteamine free-base per capsule).
Route of Administration:	Oral.
Study Procedures:	Initially, only patients who completed Study RP103-03 will be enrolled into this long-term study. Additional patients who did not complete Study RP103-03 but qualify for RP103-04 based on current inclusion and exclusion criteria may be enrolled after completion of the analysis of the RP103-03 Study where the non-inferior efficacious and safe dose of RP103 versus Cystagon® has been determined. For patients who completed Study RP103-03, study procedures include: **Screening** The RP103-04 Screening visit occurs simultaneously with the RP103-03 Period 2 Day 7 (End of Study) visit. These patients will continue RP103 Q12H treatment at the last dose level prescribed during their participation in Study RP103-03. **Monthly Study Visits** Study assessments will be made monthly (± 7 days) after study entry according to the Schedule of Events. A minimum of six (6) consecutive Monthly visits will be completed for each patient. Clinical laboratory assessments (hematology, chemistry, urinalysis), physical examination (including basic neurological and skin assessments) and vital signs, ECG, body weight, body mass index (BMI), body surface area (BSA), an Investigator administered [redacted]

	will be made according to the Schedule of Events. During these visits, blood samples for PK (cysteamine) and PD (WBC cystine) will be collected 0.5 hour post RP103 dose administered at the clinic. Patients or parents will continue to maintain a daily diary, recording the dose and time, of cysteamine medications, proton pump inhibitors (PPI) and other gastric acid reducing drugs (prescription and over the counter medications). Patients or their parents will return their completed daily diary at each scheduled study visit and will receive a new or re-dispensed daily diary. Concomitant medications and adverse events will be collected. At or before each Monthly Visit, the Investigator will review available safety and PK/PD data and if a patient does not achieve an appropriate level of WBC cystine reduction or does not tolerate the dose, the patient may have their RP103 dose adjusted or may be terminated from the Study. This review will be documented in source and in the CRF as appropriate, with the action(s) taken and reasons for such action(s). **Quarterly Study Visits** Quarterly visits will commence for each patient ≥ 1 month and < 4 months after the patient has completed 6 consecutive Monthly visits. Each Quarterly visit will take place by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15). Clinical laboratory assessments (hematology, chemistry, urinalysis), physical examination (including basic neurological and skin assessments), vital signs, ECG, body weight, body mass index (BMI), body surface area (BSA), an Investigator administered [redacted] will be made according to the Schedule of Events. During these visits, blood samples for PK (cysteamine) and PD (WBC cystine) will be collected 0.5 hour post RP103 dose administered at the clinic. Patients or parents will continue to maintain a daily diary, recording the dose and time, of cysteamine medications, proton pump inhibitors (PPI) and other gastric acid reducing drugs (prescription and over the counter medications). Patients or their parents will return their completed daily diary at each scheduled study visit and will receive a new or re-dispensed daily diary. Concomitant medications and adverse events will be collected. At or before each Quarterly Visit, the Investigator will review available safety and PK/PD data and if a patient does not achieve an appropriate level of WBC cystine reduction or does not tolerate the dose, as determined by the Investigator, the patient may have their RP103 dose adjusted or may be terminated from the Study. This review will be documented in source and in the CRF as appropriate, with the action(s) taken and reasons for such action(s).

	For patients who did not complete Study RP103-03, study procedures include: **Screening** The Screening visit may occur up to 28 days prior to Day 1. Medical and medication histories and clinical laboratory assessment (hematology, chemistry, urinalysis), physical examination (including basic neurological and skin assessments) and vital signs, ECG, body weight, body mass index (BMI), body surface area (BSA), adverse events determination, concomitant medications, an Investigator administered [redacted] will be made according to the Schedule of Events. All adult patients or parent or guardian of pediatric patients will begin completing a daily diary medication log, recording the dose and time of cysteamine medications, proton pump inhibitors (PPI) and other gastric acid reducing drugs (prescription and over the counter medications). **Dose Confirmation Period (Days 1-5)** This period includes 3 study visits over 5 days: **Day 1:** If this visit is more than 7 days after the Screening date, some assessments must be repeated as specified in the Schedule of Events. This is a morning study visit while the patient is fasted, with pre-dose (within 15 minutes prior to the first RP103 dose) blood samples collected for trough cysteamine and peak WBC cystine determination while the subject is still taking Cystagon®. RP103 treatment regimen begins at the clinic on the morning of Day 1, administered Q12H at a starting RP103 total daily dose equal to 70% of the Screening total daily dose of Cystagon®. Subjects will leave the clinic for Days 2-3 and take RP103 fasted, as instructed in Sections 9.2 and 14.8. **Days 4 and 5:** Each day includes a morning visit. 0.5 hour (30 minute) post-dose blood samples for plasma cysteamine (PK) and WBC cystine (PD) determination will be collected. RP103 Q12H treatment regimen continues at the starting total daily dose. Once the Investigator receives WBC cystine results for the Dose Confirmation Period, an RP103 dose adjustment may be prescribed so that it can be implemented before the subject returns for their next study visit (Quarterly Visit 1). **Quarterly Study Visits** Quarterly visits will take place by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and

October 15). Clinical laboratory assessments (hematology, chemistry, urinalysis), physical examination (including basic neurological and skin assessments), vital signs, ECG, body weight, body mass index (BMI), body surface area (BSA), an Investigator administered [redacted] will be made according to the Schedule of Events. During these visits, blood samples for PK (cysteamine) and PD (WBC cystine) will be collected 0.5 hour post RP103 dose administered at the clinic at each scheduled study visit. Patients or parents will continue to maintain a daily diary, recording the dose and time, of cysteamine medications, proton pump inhibitors (PPI) and other gastric acid reducing drugs (prescription and over the counter medications). Patients or their parents will return their completed daily diary at each scheduled study visit and will receive a new or re-dispensed daily diary. Concomitant medications and adverse events will be collected throughout the Study.

At or before each Quarterly Visit, the Investigator will review available safety and PK/PD data and if a patient does not achieve an appropriate level of WBC cystine reduction or does not tolerate the dose, as determined by the Investigator, the patient may have their RP103 dose adjusted or may be terminated from the Study. This review will be documented in source and in the CRF as appropriate, with the action(s) taken and reasons for such action(s).

<u>The following study procedures apply to all RP103-04 subjects, whether or not they participated in the previous Study RP103-03:</u>

Study Termination:

Patients who either complete the Study or terminate the Study early will have an End of Study (EOS) visit within 7 days (± 2 days) of their last completed study visit. Clinical laboratory assessments, physical examination, vital signs, ECG, [redacted] will be performed according to the Schedule of Events. Blood samples for PK (cysteamine) and PD (WBC cystine) will be collected 0.5 hour post RP103 dose administered at the clinic. For patients who have transitioned back to Cystagon®, PK and PD samples will be collected immediately prior to their next Cystagon® dose. Adverse events and concomitant medications will be collected.

[redacted]

	[redacted] **Other Study Procedures:** Females of child-bearing potential will provide a menstrual cycle history and be administered a serum pregnancy test at Screening (new patients only), and at each scheduled study visit. Height, weight, BMI and BSA determination will be performed at each visit according to the Schedule of Events.
Safety Assessments:	The following safety parameters will be evaluated: • Clinical laboratory tests; • Vital sign measurements; • Physical examination, basic neurological and skin assessment findings; • ECG findings; • Incidence of AEs, SAEs. In addition to clinical and laboratory assessments, patient safety will be monitored by recording adverse events (AEs) and serious adverse events (SAEs) through the Study. Any patient that becomes pregnant during the Study will be terminated from the Study and the pregnancy will be promptly reported to the Sponsor but will not be considered a SAE. If a patient has any clinically significant, Study drug-related abnormalities at the conclusion of the End of Study visit, the Investigator will determine if the patient has to be followed further. If the Investigator determines that a patient has abnormalities that require additional monitoring, the patient may be asked to return to the clinic until the abnormalities resolve or will be allowed to return home and will be followed up by telephone until resolution. AEs, whether serious or non-serious, will be followed to resolution to the extent possible regardless of whether the patient(s) is (are) still participating in the Study. Where appropriate, medical tests and examinations will be performed to document resolution of event(s). Outcome may be classified as resolved, resolved with sequelae, continuing, fatal, or unknown (lost to follow-up).
[redacted]	[redacted]

	[redacted]
Efficacy Assessments:	The following efficacy parameters will be evaluated: • 0.5 hour post dose cysteamine concentration and WBC cystine level.
Study Endpoints:	**Safety Endpoints:** • The safety profile of RP103 will be investigated by safety reviews conducted by the Investigator at or prior to each Monthly or Quarterly visit and through adverse event report monitoring (including attribution of treatment-emergent adverse events and serious adverse events [SAEs]), physical examination (including basic neurological and skin assessment findings), vital signs, ECG and clinical laboratory testing as outlined in the Schedule of Events. **Pharmacokinetic Endpoint:** • The trough plasma cysteamine concentration will be measured from samples collected 0.5 hour post dose at each study visit. **Pharmacodynamic Endpoint:** • The WBC cystine content will be measured from samples collected 0.5 hour post dose at each study visit. [redacted]**:** • [redacted]
Duration of the Study:	Patients will be followed until Study termination; which can occur by patient, physician or Sponsor request, or until the RP103 drug is available through the appropriate marketing approval, or until the Sponsor terminates development of RP103 for this indication for any reason. Approximate treatment time in the Study is up to 96 months. However, a subject may withdraw consent or be withdrawn from the study prior to completion.

Statistical Analyses:	This Study is designed to assess the long-term safety and tolerability and long-term efficacy of RP103 delayed-release cysteamine bitartrate capsules in patients with cystinosis. **Assessment Instruments:** [redacted] **Other Determinations:** Demographic and disposition data, Study drug administration, medical history, prior and concomitant medications, AEs, clinical laboratory measurements, vital signs, ECG measurements and physical examination findings will be summarized. Descriptive statistics for continuous data will include mean, standard deviation, median, min, max. For discrete data counts and percentages in each category will be tabulated. Descriptive summaries of mean and mean changes from screening will be presented for the safety laboratory parameters (hematology, serum chemistry and urinalysis, as applicable), vital signs and ECGs. The overall incidence of subjects with adverse events will be summarized by System Organ Class (SOC) and Preferred Term (PT) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Summaries by maximum severity, drug –relationship (as determined by the investigator) and drug discontinuation will also be presented. In addition, summaries of annualized exposure adjusted AE rates as well as summaries of the incidence of subjects with AEs by study year of onset (Year 1, Year 2 and Year 3 or later) will be generated. The overall incidence of subjects with serious adverse events (SAEs) will be summarized by SOC and PT. The annualized exposure adjusted SAE rates as well as the incidence by study year will also be tabulated. Safety laboratory values outside reference ranges will be flagged in laboratory listings. Non-parametric tests will be used to compare mean [redacted] domains and summary component scores over time between Screening and last acquired assessment. Trends in gastric acid reducing medications (prescription and OTC) and [redacted]

4. Introduction

4.1. Investigational Agent

Cysteamine Bitartrate Delayed-release Capsules (RP103) are a beaded, enteric-coated, delayed-release form of the bitartrate salt of cysteamine (an aminothiol, β-mercaptoethylamine), the microspheronized beads are further hard gelatin encapsulated and intended for oral administration. Cysteamine Bitartrate Delayed-release Capsules (RP103) will be available for use in this Study in 25 mg and 75 mg capsules (expressed as cysteamine free-base).

4.2. Background

Cystinosis is an autosomal recessive inborn error of metabolism in which the transport of cystine out of lysosomes is reduced or absent. Cystinosis is a rare disease characterized by the accumulation of cystine and formation of crystals damaging 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. In four studies of cystinosis patients before cysteamine was available, renal death (need for transplant or dialysis) occurred at median age of less than 10 years (Cystagon® Package Insert, 2007). Patients with cystinosis also experience growth failure, rickets, and photophobia due to cystine deposits in the cornea. With time, most organs are damaged, including the retina, muscles and central nervous system (Cystagon® Package Insert, 2007). Cysteamine is an aminothiol that reacts within lysosomes resulting in a thiol-disulfide interchange reaction that converts cystine into cysteine and cysteine-cysteamine mixed disulfide, both of which can exit the lysosome in patients with cystinosis (Cystagon® Package Insert, 2007).

Cystinosis currently affects approximately 500 people in the United States and 800 in Europe. Children with the disorder, if untreated, suffer progressive kidney failure, damage to multiple organs and a failure to grow to normal height. Most children who suffer this condition undergo kidney transplantation, typically in the first decade of life (Gahl, Balog et al. 2007). Cystagon® capsules contain cysteamine bitartrate, a cystine-depleting agent, which needs to be administered every 6 hours (Q6H) around the clock. This regimen has been associated with poor adherence. There is evidence that such failure to adhere to the strict Q6H dosing regimen results in more rapid deterioration of kidney function (Kleta, Bernardini et al. 2004) and the need for earlier hemodialysis and kidney transplantation in poorer adherent patients.

Cysteamine is moderately bound to human plasma proteins, predominantly to albumin, with mean protein binding of about 52%. Plasma protein binding is independent of concentration over the concentration range achieved clinically with the recommended doses (Cystagon® Package Insert, 2007).

The pharmacokinetics and pharmacodynamics of Cystagon® were studied in eleven pediatric patients with nephropathic cystinosis who received 225 to 550 mg of

cysteamine bitartrate every 6 hours daily for more than one year. Following repeated oral administration of 225 to 550 mg cysteamine bitartrate, the mean time to maximum plasma concentration (T_{max}) occurred at about 1.4 hours post dose with mean steady-state peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) of 2.6 µg/mL and 6.3 µg·hr/mL, respectively. The apparent volume of distribution (V/F) and apparent plasma clearance (Cl/F) of cysteamine were 156 L and 1.2 L/min, respectively (Belldina, Huang et al. 2003).

4.2.1. **Study RP103-01**

A first pilot study (i.e., Study RP103-01) was completed in order to assess the pharmacokinetics (i.e., C_{max} and T_{max}), pharmacodynamics (i.e., WBC cystine levels), safety and tolerability of Cysteamine Bitartrate Delayed-release Capsules (RP103) compared to Cystagon® in 9 patients with cystinosis. All 9 subjects (7 males, 2 females) that enrolled into the RP103-01 Study completed treatment. The average age and weight of the subjects was 12.8 (4.76) years and 36.83 (9.174) kg, respectively.

There were a total of 27 AEs reported, of which 9/27 (33.3%) were considered possibly or probably related to study drug. Twenty-five (25) of 27 (92.6 %) of AEs were mild in intensity. There was 1/27 (3.7%) moderate (abdominal pain) and 1/27 (3.7%) severe (hypokalemia) judged not related and unlikely related (respectively) to study drug. Eight (8) of 9 (88.9%) subjects experienced at least one treatment-emergent adverse event (AE). The most common AEs were thirstiness (8/27, 29.6%), vomiting (6/27, 22.2%), nausea (3/27, 11.1%) and constipation (2/27, 7.4%), and are consistent with cystinosis patients receiving cysteamine treatment. There were no study discontinuations due to an adverse event and no SAEs reported during the study.

The individual results of the non-compartmental analysis show that the pharmacokinetics of RP103 is consistent with a delayed-release formulation demonstrating a later T_{max} (i.e., 2.78 ± 1.56 and 1.22 ± 0.51 hours for RP103 and Cystagon®, respectively) and a longer half-life (5.85 ± 2.89 and 1.90 ± 0.58 hours for RP103 and Cystagon®, respectively, although the difference in half-lives might have been amplified due to truncated pharmacokinetic (PK) measurements, i.e. 0 to 6 hours for Cystagon® and 0 to 12 hours for RP103. The C_{max} for RP103 (33.06 ± 18.22 µmol/L) was also lower than the corresponding value for Cystagon® (42.02 ± 21.49 µmol/L). The plasma levels of cysteamine, determined at the end of a 12 hour dosing interval for RP103, were also considerably higher (2.89 ± 1.47 µmol/L) than those predicted for an equivalent dose of Cystagon® (~0.5 µmol/L) at 12 hours after dosing, based on its observed half-life. The $AUC_{0\text{-}12h}$ for RP103 was substantially lower than that for Cystagon® (118.2 ± 54.6 and 211.9 ± 124.6 µmol*h/L, respectively); recall that twice the Cystagon® dose is required to provide 12 hour coverage. However, the AUC_{∞} for equivalent doses of both products were similar (~120-150 µmol*h/L) suggesting that there was still exposure to cysteamine after 12 hours for RP103.

Following normalization to a 450 mg dose, the maximum plasma levels, $AUC_{0\text{-}6h}$ and $AUC_{0\text{-}12h}$ (calculated directly from the plasma level data for RP103 and from doubling the $AUC_{0\text{-}6h}$ value for Cystagon® to represent two doses) were lower for RP103 (27.70 ± 14.99 µmol/L, 75.93 ± 39.22 µmol*h/L and 99.26 ± 44.21 µmol*h/L respectively) than for Cystagon® (37.72 ± 12.10 µmol/L, 96.00 ± 37.81 µmol*h/L and 192.00 ± 75.62 µmol*h/L respectively). The dose normalized AUC_{∞}, however, was slightly higher for RP103 compared to Cystagon® (120.29 ± 50.06 and 107.35 ± 38.21 µmol*h/L for RP103 and Cystagon®, respectively) and this appeared to be largely due to the apparent longer half-life of RP103 (5.85 ± 2.89 h) compared to Cystagon® (1.90 ± 0.58 h). It was also noteworthy that the T_{max} for RP103 (2.78 ± 1.56 h) occurred later than for Cystagon® (1.22 ± 0.51 h) and as shown in **Figure 1** for averaged data.

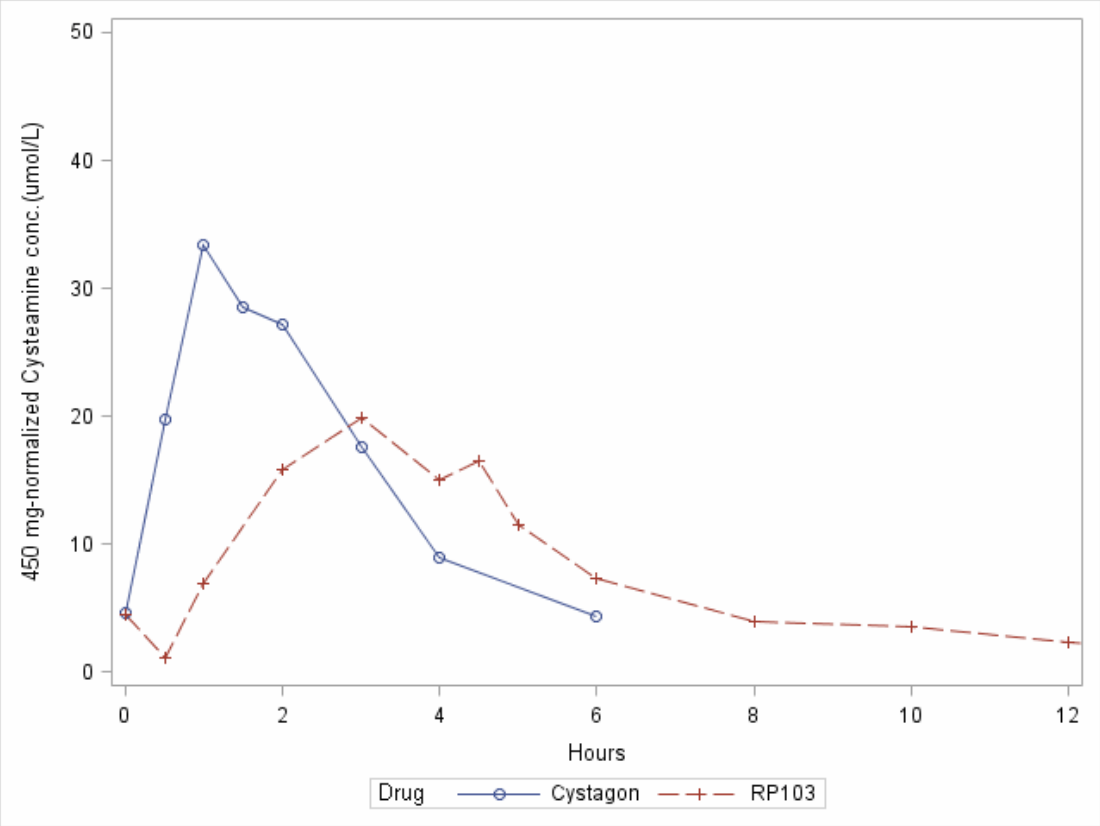

Figure 1: Mean plasma levels of cysteamine in patients receiving 450 mg oral single doses of Cystagon® and RP103

A regression of the $AUC_{0\text{-}12h}$ normalized by dose in mg/kg ($AUC\_D_{0\text{-}12h}$) for RP103 versus $AUC_{0\text{-}6h}$ normalized by dose in mg/kg ($AUC\_D_{0\text{-}6h}$) for Cystagon® (**Figure 2**) suggests a linear relationship with a slope of 1.4136. Thus, to achieve an equivalent exposure of cysteamine over a 12 hour dosing interval as measured by $AUC_{0\text{-}12h}$, a single dose of RP103 will have to be equal to 2/1.4136 = 1.4148 times a single dose of Cystagon®, which corresponds to a daily dose of RP103 equal to 70% of a daily dose of Cystagon®. As it can also be seen on this **Figure 2** when using the administered dose of Cystagon® for relating to individual AUCs, there is a poor correlation between dose

and AUC, due to a high inter-patient variability in absorption/elimination of cysteamine (highest AUCs corresponding to lowest doses for example) despite a very low intra-patient variability (AUCs after RP103 being easily predictable from AUCs after Cystagon®).

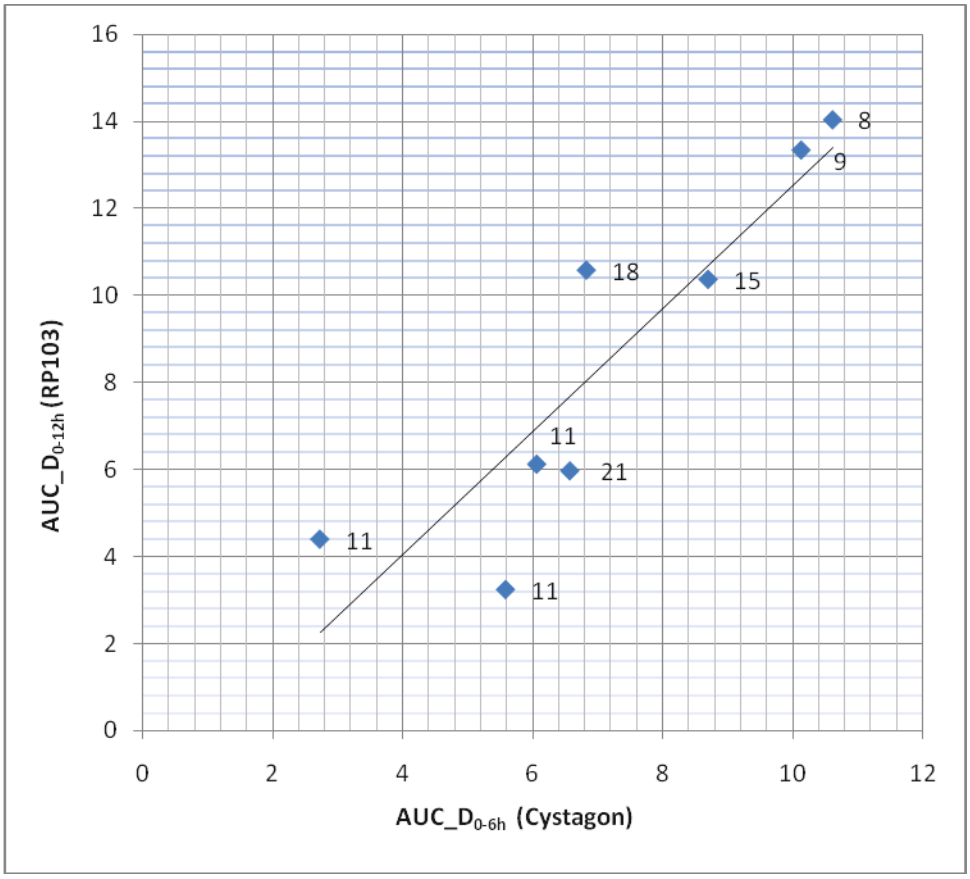

Figure 2: A regression of AUC_D$_{0\text{-}12h}$ for RP103 versus AUC_D$_{0\text{-}6h}$ for Cystagon® in patients following normalization by dose in mg/kg (diamond values represent dose at mg/kg)

Pharmacokinetic/Pharmacodynamic Relationship

An examination of the individual plots of cysteamine plasma concentrations versus time and WBC cystine levels versus time indicated little or no delay between the maximum plasma cysteamine concentration and the minimum WBC cystine level for the majority of individuals. This would be indicative of minimal hysteresis (note that due to the few number of WBC cystine measurement timepoints rigorous conclusions cannot be drawn). Thus, the plasma concentration can be directly related to WBC cystine response as presented in **Figure 3** for RP103 and Cystagon®. Furthermore, there appeared to be no difference in the cysteamine plasma concentration versus WBC cystine response between RP103 and Cystagon®. The two sets of data were, therefore, combined for the subsequent modeling to an inhibitory effect sigmoid E_{max} model. Using this model, it was estimated that the maximum decrease in WBC cystine would

be to 0.058 nmol ½ cystine/mg protein[1] starting from an initial value of 2.015 nmol ½ cystine/mg protein[2] with an EC_{50} of 2.57 nmol/L cysteamine (**Table 1**). The gamma function was close to unity at 0.921. A plot of the predicted values from the model parameters with the observed values is presented in **Figure 3.**

Table 1: Pharmacodynamic parameters using an inhibitory effect sigmoid E_{max} model for pooled data of WBC cystine response when cysteamine was administered orally as Cystagon® and RP103 to patients

Parameter	Units	Estimate	SE	CV
Starting WBC cystine level	nmol ½ cystine/mg protein[3]	2.015	0.303	15.06
EC_{50}	nmol/L	2.567	0.983	38.27
Final WBC cystine level	nmol ½ cystine/mg protein[4]	0.058	0.217	376.9
Gamma	NA	0.921	0.362	39.36

[1] Using Lowry method to determine the amount of protein used to normalize the results in mg of protein (Barshop – personal communication)
[2] Ibid
[3] Ibid
[4] Ibid

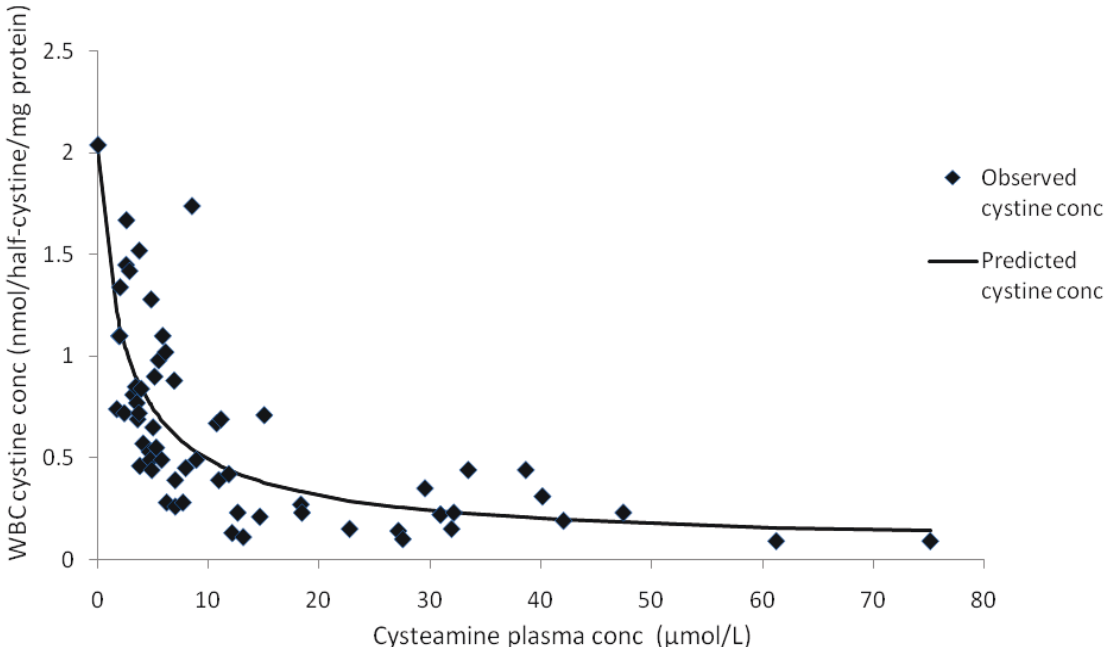

Figure 3: Predicted cystine response to oral cysteamine compared to observed response using pooled data from patients receiving Cystagon® and RP103 with an inhibitory effect sigmoid E_{max} model

4.2.2. **Study RP103-03**

This open-label, randomized, controlled crossover trial was powered to show that a new delayed-release formulation of cysteamine bitartrate, RP103, was non-inferior to the currently approved product, an immediate release cysteamine bitartrate, Cystagon®, in maintaining a surrogate marker, white blood cell (WBC) cystine as low as baseline under stable Cystagon® treatment or up to 0.3 nmol ½ cystine/mg protein greater (non-inferiority margin). Subjects were stratified by their WBC cystine baseline value (0 to 1 nmol ½ cystine/mg protein or 1 to 2 nmol ½ cystine/mg protein) before being randomized either to Cystagon® or RP103, treated for 3 weeks, and then crossed over to the other cysteamine therapy. RP103 was started at 70% of the daily dose of the Cystagon® daily dose, but could be adjusted once based on WBC cystine levels measured at the beginning of the RP103 arm of the crossover. Patients were asked to stop using proton pump inhibitors (PPIs) and any anti-acid medication while on RP103.

Forty-three (40 children and 3 adults) patients with cystinosis and with native kidney function based on an estimated GFR (corrected for body surface area) > 30 mL/minute/1.73 m^2 were randomized. Thirty-eight patients were included in the per-protocol primary efficacy analysis. Using a mixed effects statistical analysis model, the least-square-mean peak value of WBC cystine level after 12 hours under RP103 was 0.62 ± 0.05 nmol ½ cystine/mg protein and after 6 hours under Cystagon® was 0.54 ± 0.05 nmol ½ cystine/mg protein, with the difference between treatments determined as 0.08 ± 0.04 nmol ½ cystine/mg protein (95.8 % confidence interval 0 to 0.16). The average, steady-state, total daily dose of RP103 for patients completing the clinical trial was 82% of their incoming, steady-state total daily dose of Cystagon®.

Pharmacokinetic (cysteamine) and pharmacodynamic (WBC cystine) profiles after RP103 over 12 hours were comparable to PK and PD profiles after Cystagon® over 6 hours. There were no unexpected side effects compared to using Cystagon® and all patients who regularly used PPIs or antacid medication while under Cystagon® but one, were able to discontinue regular concomitant PPI or antacid medications while under RP103, which might account for the higher proportion of reported gastro-intestinal (GI) adverse events under RP103 vs. Cystagon®.

Patient Characteristics

Forty-three patients were randomized. Thirty-eight patients were included in the primary efficacy analysis, as defined beforehand in the statistical analysis plan.

The Intent-To-Treat (ITT) population has 5 more patients than the Per-Protocol (PP) population: 1) two siblings withdrew from the study because one of them had pre-study planned orthopedic surgery, unrelated to disease or treatment, and the family decided to withdraw both children related to travel difficulties; 2) three subjects had a 3-day average WBC cystine level > 2 nmol ½ cystine/mg protein during one of the periods under Cystagon® and could not therefore be considered as well controlled under Cystagon®, as pre-specified the Statistical Analysis Plan. Patients were mostly children, male or female, with an average age of almost 12 years old.

The first initiated US center enrolled slightly more patients than the other sites that were initiated afterwards. Seven patients were screened twice because the first time their WBC cystine level > 1 nmol ½ cystine/mg protein and had therefore to be terminated early. They came back after an amendment to the protocol modified this limit and allowed six of these patients with < 2 nmol ½ cystine/mg protein to be enrolled. Baseline characteristics are summarized in **Table 2**.

	ITT: Intent-To-Treat	PP: Per Protocol
N	*43*	*38*
Age (year)	11.7 ± 4.2	11.9 ± 4.4
Children (2 < age <= 12)	27	25
Adolescents (12 < age <= 21)	15	15
Adults (>21)	1	1
Male (n / %)	24 / 56 %	22 / 58 %
Height (cm)	139.5 ± 18.9	139.1 ± 19.1
Weight (kg)	36.0 ± 14.2	34.5 ± 12.1
Body Mass Index (kg/m^2)	17.8 ± 2.8	17.2 ± 2.1
Body Surface Area (m^2)	1.17 ± 0.30	1.14 ± 0.28
Daily Cystagon® Dose (mg)	1,849 ± 536	1,801 ± 511
Daily Cystagon® Dose (mg/kg)	55.8 ± 15.2	56.5 ± 14.6
WBC Cystine (nmol ½ cystine/ mg protein)		0.63 ± 0.31
WBC Cystine < 1 nmol ½ cystine/ mg protein		33 (87%)

Table 2: Baseline characteristics for all enrolled patients (ITT) and for patients (PP) well controlled (WBC < 2 nmol ½ cystine/ mg protein) during all periods under Cystagon®.

Primary Outcome, WBC cystine levels

The average peak WBC cystine level (LS mean ± SE) measured in the Per-Protocol population of patients treated with Cystagon® was 0.54 ± 0.05 nmol ½ cystine/mg protein, compared to an average peak value of 0.62 ± 0.05 nmol ½ cystine/mg protein for patients treated with RP103. The mean difference was 0.08 nmol ½ cystine/mg protein, with a 95.8% confidence interval of 0.00-0.16 (α=0.02104). This 0.16 upper end of the confidence interval was far lower than the 0.3 non-inferiority limit agreed *a priori* with FDA, determining that the study with RP103 achieved the non-inferiority endpoint. Table 3 summarizes the results of the mixed effects model regarding treatment effect on peak WBC cystine level. Based on the pre-hoc non-inferiority margin of 0.3, the new delayed-release, gastroresistant Q12H formulation of cysteamine bitartrate, RP103, was not inferior to the marketed immediate release Q6H

formulation of cysteamine bitartrate, Cystagon®, in maintaining low WBC cystine levels in patients with cystinosis.

Note: The same analysis in the ITT population with the inclusion of the 3 not-well-controlled patients under Cystagon® (i.e. who had a WBC cystine > 2 nmol ½ cystine/mg protein during the Cystagon® periods of the crossover) would have led to the conclusion that RP103 was not only non-inferior but also superior to Cystagon® with a difference of -0.27 ± 0.36, this mean difference RP103-Cystagon® being far in favor of RP103 and an upper limit of the 95.8% CI even lower (0.09 instead of 0.16) than in the PP population.

Per-Protocol (PP) Population (N=38)		
WBC Cystine (LS Mean) in mg ½ cystine/mg protein	0.54 ± 0.05	0.62 ± 0.05
Treatment Effect (LS Mean ± SE; 95% CI)	0.08 ± 0.04; 0 to 0.16	
Intent-to-Treat (ITT) Population (N=41)		
WBC Cystine (LS Mean) in mg ½ cystine/mg protein	0.97 ± 0.19	0.70 ± 0.19
Treatment Effect (LS Mean ± SE; 95% CI)	-0.27 ± 0.36; -0.63 ± 0.09	

Table 3: Treatment effect as determined by mixed effects model

Additionally, the endpoint was achieved at a lower average daily dose of RP103, compared to Cystagon®. Patients enrolled in the study were required to be "well controlled" under the existing Cystagon® therapy. The starting dose of RP103 for patients was initially set at 70% of their established dose of Cystagon®. The protocol allowed for a single RP103 dose increase of 20-25%, based on intermediate WBC cystine results, to reflect the current standard of care in establishing appropriate dosing of Cystagon® in cystinosis patients. Approximately one-third of patients who started at 70% remained at 70% of their starting Cystagon® dose throughout the study. The remaining two-thirds of these patients had their RP103 dose increased. On average, the total daily, steady-state dose of RP103 in patients in the Phase 3 clinical trial was 82% of their established, incoming dose of Cystagon®. Of 9 patients who started the study, following a protocol amendment, at 80% of their starting Cystagon® dose, one needed to have his daily dose of RP103 increased from 80% to 100% of the regular daily dose of Cystagon®.

This treatment effect on peak WBC cystine levels is further confirmed by pharmacokinetic and pharmacodynamic profiles over 6 hours after a morning dose of Cystagon® and over 12 hours after a morning dose of RP103, dosed at a lower to equivalent daily dose (70% to 100%) (see Figure 4). Patients at 90% were however treated at this level of dose not for longer than 5-8 days before final PK/PD evaluation

instead of 3 weeks, (and the recommended dose increase was not executed at all for 2 of the patients prior to endpoint analysis, even though their reported dose reflects the adjustment to 90%). A slower absorption of cysteamine due to the delayed release formulation RP103 drives the pharmacokinetics and leads to a similar peak of cysteamine as after Cystagon® but with a prolonged plateau.

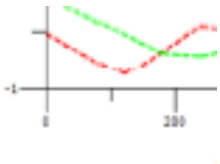

Figure 4: Mean cysteamine concentration and WBC cystine level after a single dose of Cystagon® (in red) or a single dose of RP103 (in green) in 38 patients (Per-Protocol population)

Pharmacokinetic Analysis

Mean values for principal cysteamine PK parameters after one dose under steady-state treatment with Cystagon® or RP103, peak plasma concentration C_{max}, area under the concentration-time curve over 6 hours AUC_{0-6h} for Cystagon® and 12 hours AUC_{0-12h} for RP103, T_{max}, terminal elimination half-life t½, apparent plasma clearance Cl/F and apparent volume of distribution Vd/F are listed in Table 4. Since every patient was regularly treated with a different dose of Cystagon® as determined before enrollment by their level of WBC cystine, dose-adjusted AUC_{inf} D was also calculated.

PK parameters for Cystagon® are consistent with what is described in the Cystagon® Package Insert: C_{max} = 2.6 mg/L, total exposure AUC_{0-6h} = 378 min*mg/L, T_{max} = 96 min, Cl/F = 1.2 L/min and apparent volume of distribution Vd/F = 156 L.

PK parameters for RP103 are consistent with what was observed in the first pilot RP103-01 study. As expected, since RP103 is a delayed-released formulation of the same compound, cysteamine bitartrate, as Cystagon®, T_{max} = 187 ± 89 min for RP103

is significantly longer than T_{max} = 72 ± 31 min for Cystagon®, but the apparent plasma clearances are similar, Cl/F = 1.33 ± 0.50 L/min for Cystagon® vs. Cl/F = 1.11 ± 0.58 L/min for RP103.

	Cystagon®	**RP103**
C_{MAX} (mg)	2.73 ± 1.36	3.70 ± 1.72
T_{MAX} (min)	72 ± 31	187 ± 89
$AUC_{0\text{-}12H}$ (min*mg/L)	357 ± 150	739 ± 334
T½ (min)	90 ± 23	254 ± 408
Cl/F (L/min)	1.33 ± 0.50	1.11 ± 0.58
Vd/F (L)	180 ± 112	356 ± 376
AUC_{INF}_D (min*mg/L)	0.85 ± 0.30	1.05 ± 0.45

Table 4: Principal pharmacokinetic parameters for cysteamine after a single dose at steady state

However, in order to provide further PK comparison between Cystagon® and RP103, it is important to remember that all the patients except one under RP103 received a lower daily dose than their corresponding dose of Cystagon® (most of the patients switched from 100% Cystagon® daily dose to 70% RP103 daily dose, with some who had their RP103 dose increased by 25%, and a few patients switched from 100% Cystagon® daily dose to 80% RP103 daily dose, with only one who had the RP103 dose increased to 100%, this in order to maintain a comparable WBC cystine level). This total daily dose is divided in 4 equal doses given 4 times a day for Cystagon® but divided in only 2 equal doses given 2 times a day for RP103.

As for standard of care with Cystagon®, the long-term treatment dose of RP103 to use for every patient will ultimately be determined by the peak WBC cystine level, as a resultant combination of PK and PD effect. Based on the present results, the authors would recommend that patients already well controlled under a stable daily dose of Cystagon®, be switched to an initial RP103 total daily dose equal to 70% of the (Q6H) total daily dose of Cystagon®**.** If deemed necessary based on subsequent WBC cystine measurements, the RP103 dose could be titrated up in 10% increments to reach an optimal, steady-state dose.

Anti-acid Medications

Eighteen (47%) of the thirty eight per-protocol patients in the study took proton pump inhibitors (PPIs) due to side effects from Cystagon®. Fifteen (39%) of these thirty eight patients were even on prophylactic PPI use coming into the study and/or during the Cystagon® treatment arm, meaning taking at least 1 PPI once per day. 5 patients, or 13% of total, took PPIs at some point during the RP103 treatment arm. Of these, 4 patients (11% of total) took PPIs not more than 3 times in the 3-week RP103 treatment arm. One patient (3% of total) took PPIs frequently during the RP103 treatment arm. This same patient took PPIs frequently during the Cystagon® treatment arm. One patient (3% of total) took PPIs on the RP103 treatment arm but not on the Cystagon treatment arm. This patient took PPIs not more than 3 times during the 3-week RP103 treatment arm.

Overall, PPIs were taken 453 times during the Cystagon® treatment period vs. 58 times during the RP103 treatment period. That is an 87% reduction in PPI use during identical time periods. If the one patient who took PPIs frequently on both RP103 and Cystagon® is excluded, then the reduction in PPI use was 98% (Table 5)

Number of pills / Number of patients	Cystagon	RP103
Period 1	233 / 11	51 / 2 *
Period 2	220 / 7 *	7 / 3
Total	453 / 18	58 / 5

*** Only one patient used PPIs regularly during RP103 treatment (50 pills):**
(182/6) and (1/1) = > 98% reduction

Table 5: PPI use during crossover

Safety Results

There was no unexpected serious adverse event (SAE) either under RP103 or under Cystagon®. More patients experienced at least one SAE under RP103 than under Cystagon® (respectively 6 vs. 1) but only one SAE under RP103 was considered by the Principal Investigator (PI) as possibly related to cysteamine treatment (Table 6). This

patient did not take RP103 for 2 days following the SAE, but because this SAE spontaneously resolved, the patient restarted RP103 for 2 days before being discharged from the hospital, completed the study, and was included in the 38 patients that participated to the per-protocol efficacy analysis, despite missing 2 days of treatment.

[redacted]	Treatment	Relationship to Treatment	AE Term	SAE Criteria; Issue	Outcome
[redacted]	RP103	Unrelated	Vomiting	Hospitalization; Discharged	Resolved
[redacted]	RP103	Possibly Related	Gastric Intolerance	Hospitalization; Discharged	Resolved
[redacted]	RP103	Unrelated	Right Cervical Femoral Fracture	Hospitalization; Discharged	Resolved
[redacted]	RP103	Unrelated	Elective Knee Surgery for genu valgum	Hospitalization; Discharged	Resolved
[redacted]	RP103	Unrelated	Hypokalemia	Hospitalization; Discharged	Resolved
[redacted]	Cystagon®	Unrelated	Volume Depletion	Hospitalization; Discharged	Resolved
[redacted]	RP103	Unrelated	Gastroenteritis	Hospitalization; Discharged	Resolved

Table 6: Number of unique subjects with at least one Serious Adverse Event (SAE) in all patients (ITT population)

As with Cystagon®, adverse events under RP103 were mostly nausea, vomiting and GI side effects. A total of 130 adverse events (AEs) and serious adverse events (SAEs) were reported during the trial (**Table 7** - NB: In this table some AEs are counted twice when the AE started during the Run-In period and ended during Crossover Period 1). Almost half of these AEs (59/130, 45%) were GI symptoms. Looking at the 54 GI AEs that happened during the crossover periods only, 70% (38/54) of these GI symptoms were considered by the Principal Investigator as possibly or probably related to the drug (44% RP103, 15% Cystagon® and 9% to both Cystagon® and RP103). Also, 14 of 24 (60%) drug-related GI AEs occurred in 2 patients only, which accounts for most of the difference between Cystagon and RP103 for this category of AEs.

MedDRA System Organ Class	2-week Run-In (Cystagon®)		3-week Crossover (Cystagon®)		3-week Crossover (RP103)		Both Crossover Periods	
Number of ITT patients at risk	*43*		*41*		*43*		*41*	
Number of AE Episodes	17		26		75		18	
	Related	*Not*	*Related*	*Not*	*Related*	*Not*	*Related*	*Not*
Gastrointestinal disorders	1	4	8	3	24	10	5	4
Metabolism and nutrition disorders	0	0	1	4	0	3	1	1
Nervous system disorders	0	2	0	1	2	4	0	2
Cardiac disorders	0	0	0	3	0	1	1	0
General disorders and administration site conditions	0	0	0	0	1	2	0	1
Infections and infestations	0	3	0	1	0	3	0	0
Renal and urinary disorders	0	0	0	1	1	1	1	0
Skin and subcutaneous tissue disorders	0	0	0	1	1	1	0	1
Vascular disorders	0	1	0	1	1	2	0	1
Musculoskeletal and connective tissue disorders	0	0	0	0	0	2	0	1
Respiratory, thoracic and mediastinal disorders	0	5	0	2	0	5	0	0
Injury, poisoning and procedural complications	0	1	0	0	0	3	0	0
Investigations	0	0	0	0	0	1	0	1
Ear and labyrinth disorders	0	0	0	0	0	0	0	1
Eye disorders	0	0	0	0	0	0	0	1
Psychiatric disorders	0	0	0	0	0	1	0	0

Note: Any AE starting and resolving in one of the 3 periods Run-In, Cross-Over Period 1 and Cross-Over Period 2 would be counted once for that period. Any AE starting in the Run-In and resolving in the Cross-Over period 1 would be counted once in both periods. Any AE starting either in the Run-In or in the Cross-Over treatment period 1 and resolving in the Cross-Over treatment period 2,would be counted once in the 'Both Cross-Over periods' column.

Table 7: Number of AE and SAE Episodes in all patients (ITT population)

There was no difference in terms of changes under treatment for clinical laboratory parameters between Cystagon® and RP103 during the trial.

4.2.3. **Study RP103-02**

This was a single center, bioequivalence, open-label, randomized, 2-period, 2-sequence, crossover study. The objective of this study was to compare the rate and extent of absorption of two different modes of administration of Cysteamine Bitartrate Delayed-release Capsules (RP103) following a single dose of 600 mg administered under fed conditions. The two modes of administration were: 1) intact delayed-release capsules and 2) content of opened delayed-release capsules mixed with applesauce. Due to well-known very variable bioavailability of cysteamine (Dohil, Fidler et al.

2006), a sequential design that incorporated an interim analysis after completion of Stage 1 was planned. If bioequivalence was concluded at that time, then the study would have been stopped. The study would also have been stopped if the ratio A/B for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, or C_{max} was outside the 80.00% to 125.00% boundaries. Otherwise, the study would proceed to Stage 2 with 20 additional subjects.

The pharmacokinetic (PK) parameters could not be accurately estimated following Stage 1 due to low blood concentrations of cysteamine. There appeared to be a lag time for absorption of intact capsules, as the majority of subjects did not have detectable levels of cysteamine until 6 hours after dosing, whereas more than half the subjects had detectable concentrations of cysteamine within 1 hour of dosing in the opened capsules treatment. Overall, approximately 40% of the plasma cysteamine concentrations between 0.5 and 12 hours were below the limit of quantitation for the opened capsules treatment and 72% were below the limit of quantitation for the intact capsules treatment. Therefore, the study was stopped after Stage 1 and the protocol was amended to include Stage 3. For Stage 3, four subjects already enrolled in Stage 1 were retested following the same procedures for intact capsules, but under fasted conditions. Stage 3 was conducted at the same clinical site as Stage 1, and the same protocol requirements and procedures were followed. A comparison of PK parameters obtained in the subset (n=4) of subjects who received the intact capsules treatment in fed and fasted states showed more rapid drug absorption under fasted conditions (median T_{max} of 3.25 hours versus 6.0 hours for fasted versus fed treatment). Mean C_{max} was approximately 1.8-fold higher and mean AUC was 1.6-fold higher for fasted as compared to fed subjects. Half-life was approximately 2.30 hours for both treatments. The study was stopped following Stage 3.

There were no deaths or severe adverse events reported in subjects who received single doses of RP103. No subjects were withdrawn from the study due to adverse events.

4.2.4. **Study RP103-05**

The objective of this study was to compare the rate and extent of absorption of two different modes of administration of cysteamine bitartrate delayed-release capsules (RP103) following a single dose of 600 mg administered under fasted conditions. The two modes of administration were: 1) intact delayed-release capsules and 2) content of opened delayed-release capsules.

[redacted]

Concentration data for 19 of 20 subjects who received active drug was included in the BE analysis in Periods 1 and 2. One subject was excluded from the study following Period 1 and 1 subject was excluded just prior to Period 3 due to an AE.

The rate and extent of absorption, as measured by AUC, Cmax, and Tmax, was similar

for both the opened and intact capsule treatments when administered under fasted conditions. All estimates of the ratios for the parameters AUC(0-t), AUC(0-inf), and Cmax were near 1.00, and the 94.12% confidence intervals for all comparisons were within the acceptance range for bioequivalence of 0.80 - 1.25, and there were no significant sequence or period effects observed.

Parallel-Group Meal Delay Period 3

The number of subjects in each of the 4 meal delay treatment groups ranged from 3 to 5 subjects each. A decreased rate and extent of absorption was observed for both the opened and intact capsule treatments when a meal was administered 30 minutes following drug administration compared to fasted conditions. There appeared to be no difference in AUC or Cmax between the 2 hour meal, compared with fasted conditions for the opened capsules treatment and for the intact capsules treatment.

No statistically significant treatment differences were found among the 4 meal delay treatment groups, however, this finding may be attributed to the small sample sizes of the meal delay groups.

Safety Results

There were a total of 19 AEs reported during the crossover BE portion of the study (Periods 1 and 2). One subject in each treatment group was withdrawn from the study due to an AE prior to Period 3.

The most frequently reported AEs in the crossover BE portion of the study were in the gastrointestinal (GI) disorders SOC. Gastrointestinal disorders were reported in 5 of 20 subjects (25.0%) in the opened capsule group and 3 of 19 subjects (15.8%) in the intact capsule group. The GI events were primarily single episodes of nausea and abdominal pain. One subject reported a short episode of diarrhea at approximately 64 hours following dosing in Period 1, and no subjects vomited. Seventeen out of 19 AEs in the crossover BE portion of the study were considered possibly or probably related to the study drug by the Investigator.

The most frequently reported AEs in the meal delay portion of the study were in the gastrointestinal (GI) disorders SOC. Gastrointestinal disorders were reported in 9 of 17 (52.9%) of the subjects in the meal delay portion of the study and were observed more frequently in subjects who consumed their meal 2 hours after dosing than in subjects in the 30 minute meal groups. Three of 4 subjects (75.0%) in the opened capsule/2 hour meal delay group (AM2) experienced GI AEs and 4 of 5 subjects (80.0%) in the intact capsule/2 hour meal delay group (BM2) experienced GI AEs. One subject each in the 30 minute meal delay groups experienced GI AEs. Four subjects (23.5%) vomited during the meal delay portion of the study, and 3 of the 4 subjects experienced vomiting following the 2-hour meal delay. One subject experienced severe stomach ache, headache and shakiness, and another experienced severe nausea. Treatment with ondansetron, loperamide and IV fluids were given for multiple events of vomiting or diarrhea in 2 subjects. The majority of the events began between 2 and 4 hours after dosing. Thirty-five out of 36 AEs in the crossover BE portion of the study were

considered possibly or probably related to the study drug by the Investigator.

There were no significant changes in clinical safety laboratory results, vital signs or ECGs.

4.2.5. **Study RP103-06**

Study RP103-06 was designed to demonstrate bioequivalence (BE) between oral administration of intact RP103 capsules with orange juice, and contents of opened capsules mixed with applesauce, taken orally. This was a single-center, open-label, randomized, 2 period, 2 sequence, crossover BE study. The design is identical to the previous BE study (RP103-05) with one exception: Treatment A (intact capsules) was administered with acidic juice, while Treatment B (capsule contents) was again sprinkled in a small amount of applesauce.

The outcome of Study RP103-06 was the same as for the previous BE Study RP103-05: The rate and extent of absorption, as measured by AUC, C_{max} and T_{max}, were similar for the intact and opened capsule treatments when administered under fasted conditions.

4.2.6. **Study RP103-HLTA-009**

4.3. Risk/Benefits

Cystagon® (cysteamine bitartrate) is a cystine-depleting agent that is the only cystinosis treatment approved by FDA. Cystagon® is indicated for the management of nephropathic cystinosis in children and adults. Cystagon® is contraindicated in patients who have developed hypersensitivity to it or to cysteamine or penicillamine (Cystagon® Package Insert, 2007).

The most common adverse events (> 5%) associated with cysteamine were vomiting 35%, anorexia 31%, fever 22%, diarrhea 16%, lethargy 11%, and rash 7% (Cystagon® Package Insert, 2007). Less common adverse events associated with cysteamine include: CNS symptoms such as seizures, dizziness, lethargy, somnolence, depression, and encephalopathy; gastrointestinal tract symptoms including nausea, vomiting, anorexia and abdominal pain, sometimes severe. In addition, gastrointestinal ulceration and bleeding have been reported in patients on cysteamine therapy. Cysteamine has occasionally been associated with reversible leucopenia, abnormal liver function studies, skin lesions, headache, tinnitus, diplopia, blurry vision, loss of vision, pain behind the eye or pain with eye movement (Cystagon® Package Insert, 2007).

Patient adherence with Cystagon® is challenging due to significant adverse effects, dosing frequency, and the need for life-long treatment from the age of diagnosis. Since Cystagon® must be taken Q6H around the clock; patients must be awakened in the middle of the night to take their medication in order to maintain adequate white blood

cell cystine levels. One recent study demonstrated that only about 25% (5 of 22) of patients were actually adhering to with the Q6H regimen (Levtchenko, van Dael et al. 2006). A Q6H dosing schedule must be maintained for the rest of the patient's life, therefore preventing patients and / or their caregivers from obtaining a full night's sleep. Many of these patients are in their formative years where sleep plays a major role in patient well-being and overall health. A change from Q6H to Q12H is not merely for patient convenience, as the Q6H dosing must be adhered to for an entire lifetime, there is evidence that failure to adhere to this strict Q6H dosing regimen results in rapid deterioration of kidney function (Kleta, Bernardini et al. 2004). Thus, improved patient adherence will ultimately delay the time to kidney failure or the morbidity and mortality associated with renal replacement therapy such as dialysis or transplant, and hence greatly improves both the patient's quality and quantity of life.

Patients successfully completing the RP103-03 Study will be offered the opportunity to participate in this Study (i.e., Study RP103-04).

4.4. Dose Rationale

According to results obtained from Study RP103-01, it was predicted that RP103 should be administered twice a day, where the total daily RP103 dose is 70% of the patient's total daily Cystagon® dose (see Section 4.2). Furthermore, in the RP103-01 study, a dose of RP103 up to 167% of the entry level total daily Cystagon® dose has been studied and RP103 has been found to be safe and well-tolerated.

Patients completing RP103-03 and entering this Study will have received a stable dose of either RP103 or Cystagon® prior to Screening. Patients will continue to receive their Q12H RP103 dose as determined in the phase III Study (RP103-03). Patients that did not complete the RP103-03 study but qualify for the study based on the inclusion and exclusion criteria, may be enrolled after completion of the analysis of the RP103-03 Study where the non-inferior efficacious and safe dose of RP103 versus Cystagon® has been determined. Patients that did not complete the RP103-03 study must be receiving a stable dose of Cystagon® prior to study entry and will have a starting Q12H RP103 dose at a total daily dose which is 70% of their total daily stable Cystagon® dose, administered twice a day.

If a subject does not achieve a meaningful reduction of WBC cystine level i.e., < 1 nmol ½ cystine/mg protein (see below for a discussion of this limit) or does not tolerate the dose, as determined by the Investigator, the subject may have their RP103 dose adjusted or may be terminated from the Study.

4.5. Study Rationale

Accurate measurements of intracellular cystine content are mandatory for the diagnosis and for the monitoring of the effects of cysteamine treatment. There are two components to the measurement, that for cystine content, and that for indexing the cystine content to the protein level of the cells in which it is measured.

Several methods have been developed to measure cystine content in leucocytes. They differ according to the type of cells used. Historically, cystine has been measured in mixed leucocyte preparations, despite the fact that it accumulates preferentially in polymorphonuclear granulocytes (PMNC).

Normal subjects have PMNC cystine levels lower than 0.25 nmol ½ cystine/mg protein. The diagnosis of cystinosis is confirmed when the PMNC cystine levels are > 2 nmol ½ cystine/mg protein.

Cystinosis is treated specifically using cysteamine to reduce intracellular cystine levels. Following early publications (Thoene, Oshima et al. 1976), it was thought that the PMNC cystine level should be maintained lower than 2 nmol ½ cystine/mg protein for the treatment of cystinosis with cysteamine to be effective. For patients treated with Cystagon®, leukocyte cystine measurements are useful to determine appropriate dosage and drug adherence. "When measured 5 to 6 hours after Cystagon® administration, the goal should be a level < 1 nmol ½ cystine/mg protein. In some patients with poorer tolerability for Cystagon®, patients may still receive benefit with a white blood cell cystine level of less than 2 nmol ½ cystine/mg protein" (Cystagon® Package Insert, 2007).

Variability exists in the measured cystine content in cells. Some of the variability arises from the types of cells harvested for the measurement. An even greater source of variation of the cystine level stems from the method used to determine the amount of protein used to normalize the result of the cystine assay with respect to total amount of protein in the cells. Although there is no explicit reference in the Cystagon® Package Insert as to which protein assay should be used to determine that the cystine level is less than 1 nmol ½ cystine/mg protein, the first laboratories known for measuring WBC cystine, have used the Lowry assay, which makes the Lowry assay as the method of reference, by default. The methods for the analysis of cystine and cellular total protein in white blood cells (WBC) for the current study were validated at [redacted] West Lafayette, IN under GLP principles (*good laboratory practice* or GLP specifically refers to a quality system of management controls for research laboratories and organizations to try to ensure the uniformity, consistency, reliability, reproducibility, quality, and integrity of chemical safety and efficacy tests). For that reason, [redacted] uses what is presently considered as the gold-standard assay to determine the amount of protein, the bicinchoninic acid assay (BCA) total protein method instead of the Lowry method. BCA is also used by some of the cystine determination laboratories that analyze patient samples in the US and Europe because, in addition to its being considered a more accurate assay for protein measurement, BCA is also better suited to implementing with rapid turnaround times and method robustness in a GLP compliant way than Lowry. However, during the conduct of this study, it was observed that the reported concentrations for cystine in WBC lysate from patient samples analyzed at [redacted] appeared to be consistently higher than the historical data that had been obtained previously from these patients at the cystine determination laboratories at academic medical centres that perform these assays, while on Cystagon. To address

this concern, a series of analytic experiments was initiated to determine if the GLP methods validated at [redacted] were generating results equivalent to those previously reported under the Lowry method (Powell KL, Langman CB, Pediatr Nephrol 2012).

Based on these experiments, it was determined that the Lowry vs. BCA protein results had to be adjusted as follows:

protein amount[Lowry] = protein amount[BCA] * 1.6999 - 0.0648

The correction factor ensures the patients participating in the study to receive a safe and appropriate dose of RP103 in an effort to get their WBC cystine levels similar to levels reported historically (prior to their enrollment in Raptor's clinical studies). This also allows WBC cystine results reported from the clinical studies to be consistent with all previous clinical trials and surveys, as well as with previous Cystagon® guidelines.

Regular Q6H daily treatment with Cystagon® has been shown to diminish the rate of renal dysfunction as well as promoting improved growth in children with cystinosis (Kleta, Bernardini et al. 2004). Current guidelines for following WBC cystine levels are based on obtaining blood 5 to 6 hours after the last dose of Cystagon® (Schneider 2004). White blood cell (WBC) cystine content rapidly decreases after Cystagon® ingestion, but can return to predose levels within 6 hours (Smolin, Clark et al. 1988).

RP103 dose will then be increased by approximately 10% on regular time intervals until the WBC cystine level is < 1 nmol ½ cystine/mg protein or until the patient experiences some tolerability issue.

4.6. Study Conduct

This Study will be conducted in compliance with the protocol and any amendments approved by the local Institutional Review Boards (IRBs) or Ethics Committees (ECs), and according to FDA and ICH E6 Guideline for Good Clinical Practice. The Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any change(s) to the protocol prior to seeking approval from the IRB or EC.

4.7. Study Population

Patients (male or female) with nephropathic cystinosis that successfully completed Study RP103-03 will be eligible for enrollment. Additional patients with cystinosis that did not complete the RP103-03 study but qualify for the study based on the inclusion and exclusion criteria, may be enrolled after completion of the analysis of the RP103-03 Study where the non-inferior efficacious and safe dose of RP103 versus Cystagon® has been determined.

5. Study Objectives and Endpoints

5.1. Study Objectives

The objective of this Study is to assess the long-term safety, tolerability, pharmacokinetics and pharmacodynamics of RP103 in pediatric and adult patients with cystinosis.

5.1.1. Primary Objective

- To assess safety and tolerability of long-term repeat dosing of RP103 in patients with cystinosis.

5.1.2. Secondary Objectives

- To assess the steady-state pharmacokinetics (PK) and pharmacodynamics (PD) of RP103.
- [redacted]

5.2. Study Endpoints

5.2.1. Safety Endpoints

The safety profile of RP103 will be investigated by safety reviews conducted by the Investigator at or prior to each Monthly or Quarterly visit and through adverse event report monitoring (including attribution of treatment-emergent adverse events and serious adverse events [SAEs]), physical examination (including basic neurological and skin assessment findings), vital signs, ECG and clinical laboratory testing as outlined in the Schedule of Events (Appendix 14.1).

5.2.2. Pharmacokinetic Endpoints

The trough plasma cysteamine concentration will be measured from samples collected 0.5 hour post dose at each study visit.

5.2.3. Pharmacodynamic Endpoints

The WBC cystine content will be measured from samples collected 0.5 hour post dose at each study visit.

[redacted]

6. Overall Study Design and Plan

6.1. Study Design

This is a long-term, open-label Study of the safety, tolerability and steady-state pharmacokinetics and pharmacodynamics of RP103 in pediatric and adult patients with cystinosis. Initially only patients who completed the previous phase III Study RP103-03 will be offered the opportunity to enroll in this extension Study.

Additional patients who did not complete Study RP103-03 but qualify for RP103-04 based on current inclusion and exclusion criteria may be enrolled after completion of the analysis of the RP103-03 Study where the non-inferior efficacious and safe dose of RP103 versus Cystagon® has been determined.

6.1.1. Study Visits

For patients who completed Study RP103-03, study visits consist of:

- Screening Visit: The RP103-04 Screening visit occurs simultaneously with the RP103-03 Period 2 Day 7 (End of Study) visit. These patients will continue RP103 Q12H treatment at the last dose level prescribed during their participation in Study RP103-03.
- Monthly Study Visits are only for patients who completed Study RP103-03 and will begin within 1 month (± 7 days) after study entry. Each patient will complete a minimum of 6 consecutive Monthly visits.
- Quarterly Study Visits will commence for each patient ≥ 1 month and < 4 months after the patient has completed at least 6 consecutive Monthly visits. Each Quarterly visit will take place by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15).
- End of Study (EOS) Visit will be conducted within 7 (± 2 days) from the last completed study visit or from the date of decision to terminate.

For patients who did not complete Study RP103-03, study visits consist of:

- Screening Visit which may occur up to 28 days prior to Day 1.
- Dose Confirmation Period (Days 1-5) which includes 3 study visits over 5 days.
    - Day 1 includes a morning study visit while the patient is fasted, with pre-dose blood samples collected for trough cysteamine and peak WBC cystine determination while the subject is still taking Cystagon®. RP103 treatment regimen begins at the clinic on the morning of Day 1, administered Q12H at a starting total daily RP103 dose equal to 70% of the Screening total daily Cystagon® dose. Patients will leave the clinic for Days 2-3 and take RP103 as instructed.

- Days 4 and 5 each include a morning study visit; RP103 Q12H treatment regimen continues.

- Quarterly Study Visits will commence for each patient by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15).
- End of Study (EOS) Visit will be conducted within 7 (± 2 days) from the last completed study visit or from the date of decision to terminate.

6.1.2. Study Procedures

For patients who completed Study RP103-03, study procedures include:

Screening

The RP103-04 Screening visit occurs simultaneously with the RP103-03 Period 2 Day 7 (End of Study) visit. These patients will continue RP103 Q12H treatment at the last dose level prescribed during their participation in RP103-03.

Monthly Study Visits

Only patients who completed Study RP103-03 will attend Monthly Visits. These visits will be made monthly (± 7 days) after study entry according to the Schedule of Events, Appendix 14.1. A minimum of six (6) consecutive Monthly visits will be completed for each patient. Clinical laboratory assessments (hematology, chemistry, urinalysis), physical examination (including basic neurological and skin assessments) and vital signs, ECG, body weight, body mass index (BMI), body surface area (BSA), an Investigator administered [redacted] will be made according to the Schedule of Events. During these visits, blood samples for PK (cysteamine) and PD (WBC cystine) will be collected 0.5 hour post RP103 dose administered at the clinic. Patients or parents will continue to maintain a daily diary, recording the dose and time, of cysteamine medications, proton pump inhibitors (PPI) and other gastric acid reducing drugs (prescription and over the counter medications). Patients or their parents will return their completed daily diary at each scheduled study visit and will receive a new or re-dispensed daily diary. Concomitant medications and adverse events will be collected.

At or before each Monthly Visit, the Investigator will review available safety and PK/PD data and if a patient does not achieve an appropriate level of WBC cystine reduction or does not tolerate the dose, the patient may have their RP103 dose adjusted or may be terminated from the study. This review will be documented in source and in the CRF as appropriate, with the action(s) taken and reasons for such action(s).

Quarterly Study Visits

Quarterly visits will commence for each patient ≥ 1 month and < 4 months after the patient has completed 6 consecutive Monthly visits. Each Quarterly visit will take place

by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15). Clinical laboratory assessments, clinical laboratory assessment (hematology, chemistry, urinalysis), physical examination (including basic neurological and skin assessments) and vital signs, ECG, body weight, body mass index (BMI), body surface area (BSA), [redacted] will be made according to the Schedule of Events.

During these visits, blood samples for PK (cysteamine) and PD (WBC cystine) will be collected 0.5 hour post RP103 dose administered at the clinic. Patients or parents will continue to maintain a daily diary, recording the dose and time, of cysteamine medications, proton pump inhibitors (PPI) and other gastric acid reducing drugs (prescription and over the counter medications). Patients or their parents will return their completed daily diary at each scheduled study visit and will receive a new or re-dispensed daily diary. Concomitant medications and adverse events will be collected.

At or before each Quarterly Visit, the Investigator will review available safety and PK/PD data and if a patient does not achieve an appropriate level of WBC cystine reduction or does not tolerate the dose, as determined by the Investigator, the patient may have their RP103 dose adjusted or may be terminated from the Study. This review will be documented with the action(s) taken and reasons for such action(s).

For patients who did not complete Study RP103-03, study procedures include:

Screening

The Screening visit may occur up to 28 days prior to Day 1.

Medical and medication histories and clinical laboratory assessment (hematology, chemistry, urinalysis), physical examination (including basic neurological and skin assessments) and vital signs, ECG, body weight, body mass index (BMI), body surface area (BSA), adverse events determination, concomitant medications, an Investigator administered [redacted] will be made according to the Schedule of Events, Appendix 14.1.

All adult patients or parent or guardian of pediatric patients will begin completing a daily diary medication log, recording the dose and time, of cysteamine medications, proton pump inhibitors (PPI) and other gastric acid reducing drugs (prescription and over the counter medications).

Dose Confirmation Period (Days 1-5)

This period entails 3 study visits over 5 days, required only for patients that did not complete Study RP103-03.

- **Day 1**: If this visit is more than 7 days after the Screening date, some assessments must be repeated as specified in the Schedule of Events. This is a morning study visit while the patient is fasted, with pre-dose (within 15 minutes

prior to the first RP103 dose) blood samples collected for trough cysteamine and peak WBC cystine determination while the subject is still taking Cystagon®. RP103 treatment regimen begins at the clinic on the morning of Day 1, administered Q12H at a starting RP103 total daily dose equal to 70% of the Screening total daily dose of Cystagon®.

- **Days 4 and 5:** Each day includes a morning visit. 0.5 hour (30 minute) post-dose blood samples for plasma cysteamine (PK) and WBC cystine (PD) determination will be collected. RP103 Q12H treatment regimen continues at the starting total daily dose. Once the Investigator receives WBC cystine results for the Dose Confirmation Period, and RP103 dose adjustment may be prescribed so that it can be implemented before the subject returns for their next study visit (Quarterly Visit 1).

Quarterly Study Visits

Quarterly visits will take place by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15). Clinical laboratory assessments, clinical laboratory assessment (hematology, chemistry, urinalysis), physical examination (including basic neurological and skin assessments) and vital signs, ECG, body weight, body mass index (BMI), body surface area (BSA), an Investigator administered [redacted] will be made according to the Schedule of Events.

During these visits, blood samples for PK (cysteamine) and PD (WBC cystine) will be collected 0.5 hour post RP103 dose administered at the clinic. Patients or parents will continue to maintain a daily diary, recording the dose and time, of cysteamine medications, proton pump inhibitors (PPI) and other gastric acid reducing drugs (prescription and over the counter medications). Patients or their parents will return their completed daily diary at each scheduled study visit and will receive a new or re-dispensed daily diary. Concomitant medications and adverse events will be collected.

At or before each Quarterly Visit, the Investigator will review available safety and PK/PD data and if a patient does not achieve an appropriate level of WBC cystine reduction or does not tolerate the dose, as determined by the Investigator, the patient may have their RP103 dose adjusted or may be terminated from the Study. This review will be documented in source and in the CRF as appropriate, with the action(s) taken and reasons for such action(s).

Study Termination:

Patients who either complete the Study or terminate the Study early will have an End of Study (EOS) visit within 7 days (± 2 days) of their last completed study visit. Clinical laboratory assessments, physical examination, vital signs, ECG, [redacted] will be performed according to the Schedule of Events, Appendix 14.1. Blood samples for PK (cysteamine) and PD

(WBC cystine) will be collected 0.5 hour post RP103 dose administered at the clinic. For patients who have transitioned back to Cystagon®, PK and PD samples will be collected immediately prior to their next Cystagon® dose. Adverse events and concomitant medications will be collected.

Other Study Procedures:

Females of child-bearing potential will provide a menstrual cycle history and be administered a serum pregnancy test at Screening (new patients only), and at each scheduled study visit. Height, weight, BMI and BSA determination will be performed at each visit according to the Schedule of Events.

6.2. Randomization

Patients will not be randomized.

6.3. Duration

Patients will be followed until Study termination; which can occur by patient, physician or Sponsor request, or until the RP103 drug is available through the appropriate marketing approval, or until the Sponsor terminates development of RP103 for this indication for any reason. Approximate treatment time in the Study is 96 months. However, a subject may withdraw consent or be withdrawn from the study prior to completion.

7. Selection of Subjects

7.1. Inclusion Criteria

The following criteria must be met by all subjects considered for Study participation.

7.1.1 Male and female subjects must have completed the last visit of Study RP103-03 and be willing to continue on RP103 treatment.

OR for patients who did not complete the RP103-03 study:

7.1.2 Male and female subjects with a documented diagnosis of cystinosis.
7.1.3 Subjects must be on a stable dose of Cystagon® at least 21 days prior to Screening.
7.1.4 [no longer applicable]
7.1.5 Within the last 6 months, no clinically significant change from normal in liver function tests [i.e., 1.5 times ULN for ALT and AST, and/or 1.5 times ULN for total bilirubin] and renal function [i.e., estimated GFR (corrected for body surface area)] at Screening as determined by the Investigator.
7.1.6 Subjects must have an estimated GFR (corrected for body surface area) > 30 mL/minute/1.73 m^2.

7.1.7 Sexually active female subjects of childbearing potential (i.e., not surgically sterile [tubal ligation, hysterectomy, or bilateral oophorectomy] or at least 2 years naturally postmenopausal) must agree to utilize the same acceptable form of contraception from Screening through completion of the Study. The acceptable forms of contraception for this Study include hormonal contraceptives (oral, implant, transdermal patch, or injection) at a stable dose for at least 3 months prior to Screening, barrier (spermicidal condom, diaphragm with spermicide), IUD, or a partner who has been vasectomized for at least 6 months. For pre-pubescent children, a documented attestation of abstinence from their parent or guardian will be acceptable.

7.1.8 Subject must be willing and able to comply with the Study restrictions and requirements.

7.1.9 Subject or their parent or guardian must provide written informed consent and assent (where applicable) prior to participation in the Study.

7.2. Exclusion Criteria

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

AND for patients who did not complete the RP103-03 study:

7.2.2. Subjects less than 1 year old.

7.2.3. Subjects with current history of the following conditions or any other health issues that make it, in the opinion of the Investigator, unsafe for them to participate:

- Inflammatory bowel disease (if currently active) or prior resection of small intestine;
- Heart disease (e.g., myocardial infarction, heart failure, unstable arrhythmias, or poorly controlled hypertension) 90 days prior to Screening;
- Active bleeding disorder 90 days prior to Screening;
- History of malignant disease within the last 2 years.

7.2.4. Subject with a hemoglobin level of < 10 g/dL at Screening or, in the opinion of the Investigator, a hemoglobin level that would make it unsafe for the subject to participate.

7.2.5. [no longer applicable]

7.2.6. Subjects with known hypersensitivity to cysteamine and penicillamine.

7.2.7. Female subjects who are nursing, planning a pregnancy, known or suspected to be pregnant, or with a positive serum pregnancy screen.

7.2.8. Subjects who, in the opinion of the Investigator, are not able or willing to comply with the protocol.

7.3. Removal of Subjects from Study Participation

Subjects will be informed that they are free to withdraw from the Study at any time and for any reason. The Investigator may remove a subject from the Study if, in the Investigator's opinion, it is not in the best interest of the subject to continue the Study. Subjects may be discontinued due to the following: change in compliance with inclusion/exclusion criteria(ion) that is(are) clinically relevant and affects subject safety, occurrence of AEs that result in the subject or the Investigator requesting a Study withdrawal, occurrence of pregnancy, intake of non-permitted concomitant medication that might affect subject safety or Study assessments/objectives, etc.

Notification of discontinuation will immediately be made to the Sponsor's representative(s). In case of premature discontinuation of Study participation, efforts will be made to have the subject return to the clinic for a follow-up visit within 7 ± 2 days of last study drug administration and perform all Follow-up/Study termination assessments [see Schedule of Events (Appendix 14.1)]. The date the subject is withdrawn from the Study and the reason for discontinuation will be recorded on the subject's CRF. All dropouts will be followed until resolution of any AEs or until the unresolved AEs are judged by the Investigator to have stabilized. For subjects who are discontinued by the Investigator or who voluntarily withdraw prematurely from the Study, replacement subjects may be enrolled at the discretion of the Sponsor.

Subjects may be withdrawn from the Study for the following reasons:

- Illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Subject decides to withdraw from the Study;
- General or specific changes in the subject's condition render further treatment unacceptable for the Subject in the judgment of the Investigator;
- Protocol non-compliance;
- Cancellation of drug development;
- Request from IRB, Ethics Committee or regulatory agency.

8. Treatment of Subjects

8.1. Study Treatment

The Sponsor, or designee, will provide the Investigator with adequate quantities of the RP103. The active ingredient in RP103 is cysteamine bitartrate; dosage is expressed as mg of cysteamine free base (see Table 8).

Table 8: Study Drugs

Study Drug	Cysteamine Bitartrate Delayed-release Capsules (RP103)
Form[a]	Capsules
Strength[b]	75 mg and 25 mg
[redacted]	[redacted]

[redacted]	[redacted]

[a] Specific ingredients/purity will be identified on the Certificate of Analysis (or equivalent) that is supplied for RP103.

[b] Provided strength is as cysteamine free base.

8.2. Identity of Investigational Products

The 25 mg strength Cysteamine Bitartrate Delayed-release Capsules (RP103, test product) are a size [redacted] in white ink. They are provided in 60-count bottles.

The 75 mg strength Cysteamine Bitartrate Delayed-release Capsules [redacted] in white ink. They are provided in 150-count bottles.

8.3. Storage of Investigational Products

Cysteamine Bitartrate Delayed-release Capsules (RP103) should be stored at the conditions specified in the current study pharmacy manual.

8.4. Concomitant Medications and Excluded Therapies

All patients will be asked about concomitant medications at study entry and at each study visit. For patients entering the Study on a chronic concomitant medication, adequate clarification of the reason for taking that medication must be documented in source documentation (e.g., medical history). Information about medications used during after study entry must also be recorded. Patients must observe the restrictions listed here for the specified time periods and throughout the study.

Patients entering the Study on Cystagon® will be asked to stop gastric acid reducing medications at least 12 hours before receiving their first dose of RP103 until Study termination. In cases of intolerable gastric upset, gastric acid reducing medications will be allowed, at the discretion of the Investigator. All gastric upset adverse events will be captured and recorded. All concomitant medications used to treat adverse events should be captured and recorded appropriately.

At Screening, the patient or parent will be provided with a daily diary to record protocol specified cysteamine medications, proton pump inhibitors (PPI) and other gastric acid reducing drugs, including over the counter gastric acid reducing medications, and instructed on its completion. At each clinic visit, the staff will review the diary for completion, collect completed diaries and re-dispense or issue a new one. Continued non-compliance with the diaries may be considered a reason for early Study termination. All diaries will be collected at Study completion.

Illegal or recreational alcohol or drug use is not allowed during the study. If the Investigator suspects illegal or recreational alcohol or drug use, alcohol or drug tests may be administered at the discretion of the Investigator.

8.5. Study Treatment Administration and Compliance

All study treatments administered in the clinic will be under the supervision of clinic personnel. Patients not entering the trial from Study RP103-03 will be started on twice a day administration of RP103, where the total daily RP103 dose is 70% of their total daily stable Cystagon® dose.

If during the study any patient does not achieve a meaningful reduction of WBC cystine level (i.e., < 1 nmol ½ cystine/mg protein) or does not tolerate the dose, as determined by the Investigator, the patient may have their RP103 dose adjusted or may be terminated from the study.

A daily diary of cysteamine and gastric acid reducing medications will be maintained throughout the study.

9. Study Procedures

Before any Study-specific procedures are performed, the patient and legal guardian (if appropriate) must receive an explanation of all Study procedures and must sign and date an Institutional Review Board (IRB) or Ethics Committee (EC)-approved written informed consent and assent (if applicable) form.

9.1. Schedule of Study Procedures

9.1.1. Screening

<u>For patients who completed Study RP103-03:</u>

- The following data can be obtained from the RP103-03 Screening visit:
  - Demographics.
  - Medical history.
  - Medication history.
  - Menstrual history for females of childbearing potential.
- The following data can be obtained from the RP103-03 Termination visit:
  - Clinical laboratory
  - Physical examination
  - 12-lead ECG
  - Vital signs
- Dispense RP103 study medication.
- Schedule return clinic visit for Monthly Visit 1.

For patients who did not complete Study RP103-03:

- Review inclusion/exclusion criteria.
- Record demographics.
- Record medical history.
- Record medication history.
- Record menstrual history for females of childbearing potential.
- Perform a physical examination (see Section 9.10).
- Obtain clinical laboratory samples (serum chemistry, hematology, and urinalysis, see Section 9.7).
- Collect a cysteamine PK sample pre-dose RP103 administration. Actual collection time will be recorded.
- Collect a WBC cystine PD sample pre-dose RP103 administration (which should be 5-6 hours post last Cystagon® administration). Actual collection time will be recorded.
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature, see Section 9.11).
- Obtain a 12-lead ECG (see Section 9.9).
- Provide training for Daily Diary log of cysteamine and gastric acid reduction medications. Provide copy of daily medication diary.
- Schedule return clinic visits for Days 1, 4 and 5.

For all patients:

- Obtain serum pregnancy test from females of childbearing potential.
- Measure height and weight.
- Calculate BMI and BSA (see Appendix 14.5).
- [redacted]
- [redacted]
- Prepare subjects for study participation by informing them of study restrictions and procedures.
- Provide copy of daily medications diary.
- Record concomitant medications.
- Monitor AEs.

For patients whose Screening visit was > 7 days prior to Day 1, complete the following prior to RP103 dosing:

- Re-assess inclusion/exclusion criteria.
- Record any changes since Screening to medical history, medication history, menstrual history for females of childbearing potential.
- Obtain serum pregnancy test from females of childbearing potential.
- Measure height and weight.
- Calculate BMI and BSA (see Appendix 14.5).
- Perform a physical examination (see Section 9.10).
- Collect a cysteamine PK sample pre-dose RP103 administration. Actual collection time will be recorded.
- Collect a WBC cystine PD sample pre-dose RP103 administration. Actual collection time will be recorded.
- Obtain clinical laboratory tests (serum chemistry, hematology, and urinalysis, see Section 9.7).
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature, see Section 9.11).
- Obtain a 12-lead ECG approximately 3 hours (± 15 minutes) post RP103 administration (see Section 9.9).
- [redacted]
- [redacted]
- Record concomitant medications.
- Monitor AEs.

9.1.2. Day 1 Study Visit (only for patients who did not complete Study RP103-03)

- Collect and review completed diary.
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature).
- Subjects should be fasting for at least 2 hours prior to the following blood sample collections and subsequent RP103 dosing.
    - Collect a cysteamine PK sample pre-dose RP103 administration. Actual collection time will be recorded.
    - Collect a WBC cystine PD sample pre-dose RP103 administration. Actual collection time will be recorded.

- Administer a Q12H dose of RP103 with a starting total daily RP103 dose equal to 70% of their total daily Cystagon® dose. Study drug should be administered with an acceptable food or liquid as described in Appendix 14.9.
- A meal or snack will be ingested between 30 and 60 minutes after RP103 dosing.
- Obtain a 12-lead ECG approximately 3 hours (± 15 minutes) post RP103 administration (see Section 9.9).
- Record concomitant medications.
- Monitor AEs.
- Dispense RP103 and instructions for home administration.
- Confirm return clinic visits for Days 4 and 5.

9.1.3. Day 4 and Day 5 Study Visits (only for patients who did not complete Study RP103-03)

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature).
- Subjects should be fasting for at least 2 hours prior to RP103 dosing.
- Collect a cysteamine PK sample 0.5 hour (30 minutes) post-dose RP103 administration. Actual collection time will be recorded.
- Collect a WBC cystine PD sample 0.5 hour (30 minutes) post-dose RP103 administration. Actual collection time will be recorded.
- Administer a Q12H dose of RP103 with a starting total daily RP103 dose equal to 70% of their total daily Cystagon® dose. Study drug should be administered with an acceptable food or liquid as described in Appendix 14.9.
- A meal or snack will be ingested between 30 and 60 minutes after RP103 dosing.
- Record concomitant medications.
- Monitor AEs.
- Dispense RP103 and instructions for home administration.
- Schedule return clinic visit for Quarterly Visit 1.

9.1.4. Monthly (± 7 days) Study Visit (only for patients who completed Study RP103-03)

- Collect and review the completed diary.
- Obtain serum pregnancy test (females of childbearing potential).
- Perform physical examination (see Section 9.10).

- Measure height and weight.
- Calculate BMI and BSA (see Appendix 14.5).
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature, see Section 9.11) within 30 minutes prior to RP103 administration.
- Obtain clinical laboratory tests (serum chemistry, hematology, and urinalysis, see Section 9.7) prior to RP103 administration.
- Obtain a 12-lead ECG (see Section 9.9).
- Subjects should be fasting for at least 2 hours prior to RP103 dosing.
- A meal or snack will be ingested between 30 and 60 minutes after RP103 dosing.
- Administer Q12H RP103 dose with an acceptable food or liquid as described in Appendix 14.9.
- Collect a cysteamine PK sample 0.5 hour (30 minutes) post RP103 dose administration. Actual collection time will be recorded.
- Collect a WBC cystine PD sample 0.5 hour (30 minutes) post RP103 dose administration. Actual collection time will be recorded.
- [redacted]
- [redacted]
- Dispense RP103 for home administration.
- Dispense new diary.
- Record concomitant medications.
- Monitor AEs.
- Schedule return clinic visit.

Perform a safety and PK/PD review prior to or at the study visit. If a patient does not achieve a meaningful reduction of WBC cystine level (i.e., < 1 nmol ½ cystine/mg protein) or does not tolerate the dose, as determined by the Investigator, the patient may have their RP103 dose adjusted or may be terminated from the Study.

9.1.5. Quarterly (± 7 days) Study Visit

- Collect and review completed diaries.
- Obtain serum pregnancy test (females of childbearing potential).
- Perform physical examination (see Section 9.10).
- Measure height and weight.
- Calculate BMI and BSA (see Appendix 14.5).

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature, see Section 9.11) within 30 minutes prior to RP103 administration.
- Obtain clinical laboratory tests (serum chemistry, hematology, and urinalysis, see Section 9.7) prior to RP103 administration.
- Obtain a 12-lead ECG (see Section 9.9).
- Subjects should be fasting for at least 2 hours prior to RP103 dosing.
- A meal or snack will be ingested between 30 and 60 minutes after RP103 dosing.
- Administer Q12H RP103 dose with an acceptable food or liquid as described in Appendix 14.9.
- Collect a cysteamine PK sample 0.5 hour (30 minutes) post RP103 dose administration. Actual collection time will be recorded.
- Collect a WBC cystine PD sample 0.5 hour (30 minutes) post RP103 dose administration. Actual collection time will be recorded.
- [redacted]
- [redacted]
- Dispense RP103 for home administration.
- Dispense new diary.
- Record concomitant medications.
- Monitor AEs.
- Schedule return clinic visit.

Perform a safety and PK/PD review prior to or at the study visit. If a patient does not achieve a meaningful reduction of WBC cystine level (i.e., < 1 nmol ½ cystine/mg protein) or does not tolerate the dose, as determined by the Investigator, the patient may have their RP103 dose adjusted or may be terminated from the Study.

9.1.6. End of Study Visit (7 ± 2 days after last study visit or decision to terminate)

<u>For all patients:</u>

- Collect and review completed diary.
- Perform physical examination (see Section 9.10).
- Measure height and weight.
- Calculate BMI and BSA (see Appendix 14.5).
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature, see Section 9.11).
- Obtain clinical laboratory tests (serum chemistry, hematology, and urinalysis, see Section 9.7).
- Obtain a 12-lead ECG (see Section 9.9).
- [redacted]

- Administer the VAS measurement of swallowing difficulty (see Section 9.13).
- Record concomitant medications.
- Monitor AEs.

For patients still receiving RP103 treatment:

- Subjects should be fasting for at least 2 hours prior to RP103 dosing.
- A meal or snack will be ingested between 30 and 60 minutes after RP103 dosing.
- Administer Q12H RP103 dose with an acceptable food or liquid as described in Appendix 14.9.
- Collect a cysteamine PK sample 0.5 hour (30 minutes) post RP103 dose administration. Actual collection time will be recorded.
- Collect a WBC cystine PD sample 0.5 hour (30 minutes) post RP103 dose administration. Actual collection time will be recorded.

For patients that terminated from the Study and transitioned onto Cystagon® treatment:

- Collect a cysteamine PK sample immediately prior to their next Cystagon® dose administration. Actual collection time will be recorded.
- Collect a WBC cystine PD sample immediately prior to their next Cystagon® dose administration. Actual collection time will be recorded.

If a subject has any clinically significant, Study drug-related abnormalities at the conclusion of the study termination, the Investigator will determine if the subject has to be followed further. If the Investigator determines that a subject has abnormalities that require additional monitoring, the subject may be asked to return to the clinic until the abnormalities resolve or will be allowed to return home and will be followed up by telephone until resolution. If the subject is to be followed up, the Medical Monitor (or designated representative) should be notified. Every effort should be made to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

[redacted]

9.2. Fluid and Dietary Control

Data from studies RP103-02 (see Section 4.2.3) and RP103-05 (see Section 4.2.4) in healthy volunteers suggests a significant food effect on cysteamine absorption: the more food that is taken around cysteamine dosing, the less the fractional absorption of cysteamine is observed (Figure 5) and the more variable is this absorption (Figure 6). This food effect had been anecdotally noticed in one patient taking Cystagon® (Smolin,

Clark et al. 1988) but no other publication about the subject could be found, despite the recommendation by the Agencies of taking Cystagon® with food to decrease GI effects.

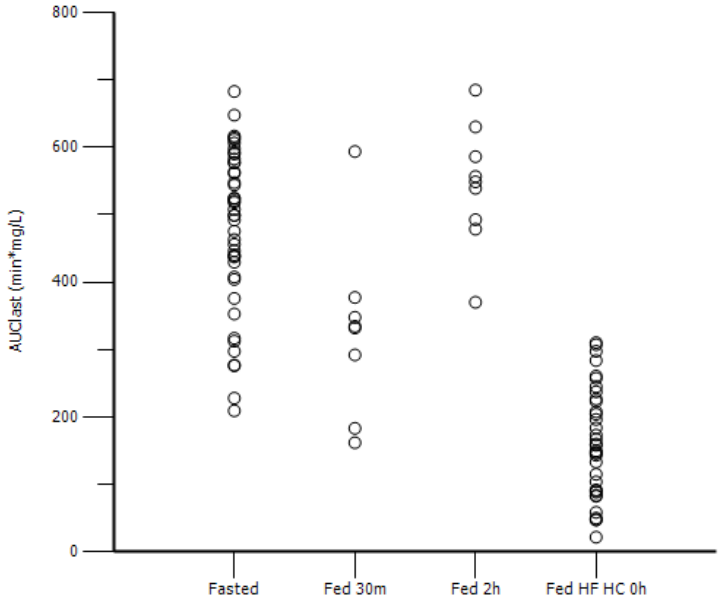

Figure 5: Quantity of absorbed cysteamine (AUC) vs. Food: Fasted [10 hours before – 4 hours after], Fed 30 m [fasted 10 hours before, normal meal 1/2h after dosing], Fed 2 h [fasted 10 hours before, normal meal 2h after dosing], Fed high fat / high caloric [HF HC] 0h [meal at dosing time]

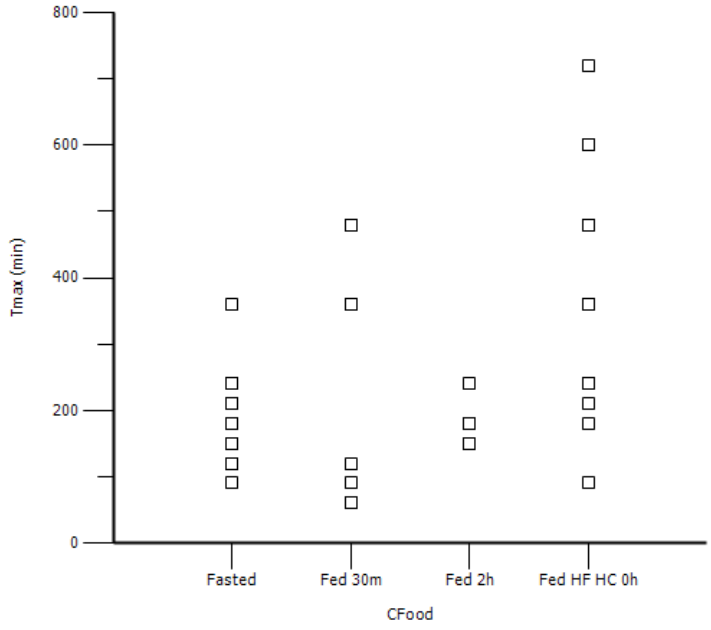

Figure 6: Time to peak of absorbed cysteamine (T_{max}) vs. Food: Fasted [10 hours before – 4 hours after], Fed 30 m [fasted 10 hours before, normal meal 1/2h after dosing], Fed 2 h [fasted 10 hours before, normal meal 2h after dosing], Fed high fat / high caloric [HF HC] 0h [meal at dosing time]

In patients, as predicted by the inhibitory E_{max} pharmacodynamic model (see Figure 3), the more variable the absorption of cysteamine, the more variable is the peak of WBC cystine level (some measurements being then > 1 nmol ½ cystine/mg protein).
This food effect may explain the intermittency of GI side effects observed in patients with cystinosis treated with Cystagon® (Elenberg, Norling et al. 1998): for those patients who are regularly taking cysteamine with a significant amount of food, their dose of cysteamine, adjusted based on their peak of WBC cystine level, is significantly higher than if they were taking cysteamine fasted, and with an increased risk of side effects on the days where they would eat significantly less than usual.

In these studies in healthy volunteers, very few and only minor GI side-effects were seen when subjects ingested RP103 while fasted. Therefore Raptor recommends as best practice for patients to try to avoid food for 2 hours before and at least 30 minutes after RP103 administration. In case patients cannot comply with this recommendation, patients should ingest only a small amount of food around the time of RP103 dosing (from 1 hour before to 1 hour afterwards) and importantly, withhold dairy products during this time window.

RP103 should be administered with an acceptable food or liquid as described in Appendix14.9 RP103 Dosing Instructions, and not with water. During study visits, food will be available for the patient to eat at between 30 and 60 minutes after taking study medication while at the clinic in a (2h) fasted state.

9.3. Contraception and Hormone Therapy

9.3.1. Women

For women subjects who did not already provide this information during RP103-03, they will be asked about their menstrual cycle history (including date of last period; menses regularity; typical duration and normalcy; any abnormal discharges; and excessive bleeding).

Women of childbearing potential who are sexually active must be non-lactating and have a negative serum pregnancy test at Screening and use any one of the following acceptable methods of contraception until Study termination:

- Hormonal contraceptives (oral, implant, transdermal patch, or injection) at a stable dose for at least 3 months prior to Screening.
- Placement of copper-containing intrauterine device (IUD).
- Spermicidal condoms.

- Diaphragm with spermicide.
- Male partner who has had a vasectomy for at least 6 months.

Women of non-childbearing potential who have a negative serum pregnancy test at Screening must also meet at least 1 of the following criteria:

- Be postmenopausal, defined as having been amenorrheic for least 2 years and a serum follicle-stimulating hormone (FSH) >30 IU/L.
- Have had a hysterectomy, a bilateral oophorectomy or tubal ligation.
- If child is pre-pubescent, documented attestation of abstinence from their parent or guardian or documentation by the investigator that abstinence has been discussed with the subject, parent or guardian.

9.3.2. Men

All men who have not had a vasectomy and their partners will be asked to practice appropriate contraception, as described above, during the Study.

9.4. Pharmacokinetic Blood Sample Collecting and Processing

Plasma PK samples will be collected at the timepoints specified in the Schedule of Events (see Appendix 14.1). Blood can be drawn by separate venipunctures, indwelling catheters, peripherally inserted central catheter (PICC) line or by combinations of these or other suitable methods. The indwelling or PICC line should be managed as prescribed by the clinic procedures. Collection and processing instructions can be found in Appendix 14.6.

9.5. Pharmacodynamic Blood Sample Collecting and Processing

Blood samples for WBC cystine determination will be collected at the timepoints specified in the Schedule of Events (see Appendix 14.1). Blood can be drawn by separate venipunctures, indwelling catheters, peripherally inserted central catheter (PICC) line or by combinations of these or other suitable methods. The indwelling or PICC line should be managed as prescribed by the clinic procedures. Collection and processing instructions can be found in Appendix 14.7. Priority for blood sampling should be given to blood collected for WBC cystine determination.

9.6. Analytical Methodology

Plasma cysteamine concentration will be determined using methods employing Hydrophilic Interaction Liquid Chromatography (HILC) high pressure liquid chromatography (HPLC) tandem mass spectrometry (HPLC-MS/MS) (Dalton and Turner 2005; Dohil, Fidler et al. 2006). White blood cell (WBC) cystine concentration will be determined using high performance liquid chromatography-electrospray

ionization tandem mass spectrometry (LC-ESI-MS/MS) (Dalton and Turner 2005; Dohil, Fidler et al. 2006).

9.7. Clinical Laboratory Evaluations

Clinical laboratory (hematology and chemistry) and urinalysis will be performed according to the Schedule of Events (see Appendix 14.1). [redacted] Females of childbearing potential will provide a serum sample for a pregnancy testing during Screening at each study visit.

Clinical safety laboratory tests will be performed by a central laboratory. For patient safety, clinical laboratory samples to manage patient adverse events may be analyzed using the clinic's local laboratory. **Table 9** summarizes tests that will be performed.

The Investigator will monitor the laboratory test findings. If any laboratory test on or after the first study drug treatment is abnormal, it will be followed at the discretion of the Investigator. Abnormal laboratory tests, including ECGs, may, in the opinion of the Investigator, be considered clinically significant and, thus, constitute or be associated with an AE. In such cases, they must be reported on the AE page of the CRF. Any abnormal clinical lab that is determined not to be clinically significant will have a description of the reason for this determination documented on the lab CRF.

Table 9: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Hematocrit	Alanine aminotransferase	Bilirubin
Hemoglobin	Albumin	Blood (qualitative)
Mean corpuscular hemoglobin	Aspartate aminotransferase	Color
Mean corpuscular hemoglobin concentration	Alkaline phosphatase	Glucose
Mean corpuscular volume	Amylase	Ketones
Erythrocytes	Conjugated bilirubin	Leukocyte esterase
Red cell distribution width	Total bilirubin	Nitrite
Platelet count	Blood urea nitrogen	pH
Leukocytes	Calcium	Protein
Differential (absolute, %)	Bicarbonate	Specific gravity
Basophils	Chloride	Turbidity
Eosinophils	Total cholesterol	Urobilinogen
Lymphocytes	Creatinine	Microscopic examination
Monocytes	Gamma glutamyl transpeptidase	
Neutrophils	Glucose	
Reticulocyte count	Lactate dehydrogenase	
	Phosphorus	
	Potassium	
	Total protein	
	Sodium	
	Triglycerides	

	Uric acid	
Other Laboratory Tests		
Serum pregnancy test	Human chorionic gonadotropin as applicable	

9.8. Blood Volume

Assuming the approximate participation of 96 months, the estimated volume of blood drawn (in mL) per subject is provided below, for subjects who did participate in the previous pivotal Study RP103-03 and for those who did not (i.e. enrolled under RP103-04 Protocol Amendment 5). The total blood volume for quarterly visits is proportionate to the number of visits completed. The maximum number of visits is listed in the tables below.

RP103-03 Study Completers

Study Visit	**Maximum # Visits**	**Chemistry & Hematology**	**PK**	**PD**	**Pregnancy**	**TOTAL** without pregnancy tests	**TOTAL** with pregnancy tests
Screening	1	4.5 mL	1.0 mL	4.0 mL	0.5 mL	9.5 mL	10 mL
Monthly Visits	9	4.5 mL	1.0 mL	4.0 mL	0.5 mL	85.5 mL	90 mL
Quarterly Visits	30	4.5 mL	1.0 mL	4.0 mL	0.5 mL	285 mL	300 mL
Study Exit Visit	1	4.5 mL	1.0 mL	4.0 mL	0.5 mL	9.5 mL	10 mL
						389.5 mL	**410 mL**

RP103 Naïve (subjects enrolled under RP103-04 Protocol Amendment 5)

Study Visit	**Maximum # Visits**	**Chemistry & Hematology**	**PK**	**PD**	**Pregnancy**	**TOTAL** without pregnancy tests	**TOTAL** with pregnancy tests
Screening Visit	1	4.5 mL	1.0 mL	4.0 mL	0.5 mL	9.5 mL	10 mL
Day 1	1	4.5 mL	1.0 mL	4.0 mL	0.5 mL	9.5 mL	10 mL
Day 4	1	4.5 mL	1.0 mL	4.0 mL	0.5 mL	9.5 mL	10 mL
Day 5	1	4.5 mL	1.0 mL	4.0 mL	0.5 mL	9.5 mL	10 mL
Quarterly Visits	32	4.5	1.0	4.0	0.5	304 mL	320 mL
Study Exit Visit	1	4.5	1.0	4.0	0.5	9.5 mL	10 mL
						351.5 mL	**370 mL**

For any subject who participates in the optional PK substudy an additional 18 mL will be collected (over a 12 hour period).

If the Investigator suspects alcohol or drug abuse, additional urine or blood samples may be collected.

9.9. 12-Lead Electrocardiograms

Standard 12-lead ECGs will be used for the ECG evaluation. All scheduled ECGs should be performed after the subject has rested quietly in the supine position for at least 5 minutes. A single, 10-second, 12-lead ECG will be obtained on all subjects as shown in the Schedule of Events (see Appendix 14.1). All ECGs will be retained as a paper copy in the subject's source records. The ECGs will be recorded at the specified timepoints at a speed of 25 mm/sec and amplitude of 10 mm/mV.

To ensure safety, a qualified individual at the clinic will review the ECGs. If an abnormality is noted, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement. It is important that leads be placed in approximately the same positions each time to achieve precise ECG recordings. If a machine-read ECG is found to be abnormal, repeat measurements may not be necessary if a qualified physician's interpretation determines that the abnormality noted on the machine reading is not clinically significant. Any such determination will be recorded with the reason for the assessment on the eCRF.

ECGs will be recorded on appropriate and standardized ECG recorders. Built-in computer algorithms may be used to facilitate ECG interpretation and measurement of intervals.

9.10. Physical Examinations

Physical examinations will be performed according to the Schedule of Events (see Appendix 14.1). The physical examination will include assessments of the following: general appearance, eyes, ears, nose and throat, chest (heart, lungs), abdomen (palpation, GI sounds), extremities and skin. The Investigator will also conduct a basic neurological examination.

9.11. Vital Signs

Blood pressure may be measured in the seated position. Screening blood pressure may be retested 3 times at intervals of no less than 5 minutes between each measurement. Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, and oral body temperature) will be measured according to the Schedule of Events (see Appendix 14.1). Blood pressure will be measured with the arm supported at the level of the heart, and recorded to the nearest 1 mm Hg. The subject should be at rest for at least 5 minutes before the blood pressure is measured. The use of automated devices for measuring blood pressure and heart rate are acceptable. When done manually, heart rate will be measured in the brachial or radial artery for at least 30 seconds.

9.12. Adverse Event Inquiries

Spontaneous adverse event reports will be identified initially by an open-ended, nondirective question. This inquiry can be collected while vital signs are being collected or at other appropriate timepoints during the study visit.

[redacted]

[redacted]

9.15. Product Accountability

Cysteamine Bitartrate Delayed-release Capsules (RP103) will be supplied by the Sponsor or its representative. The Investigational Pharmacy will record the lot numbers. Accountability will be performed on the clinical trial supply. The Investigator or a designee will verify and acknowledge receipt of the RP103 by signing and returning all required forms. All medication must be stored in a secured area under the proper storage requirements with access restricted to the Investigator or designees. Medication designated for this clinical Study must not be administered to any subjects other than those enrolled in this specific investigation and may not be used for any laboratory or animal research. All medication dispensed to subjects must be properly labeled and accurately recorded on the drug accountability records maintained at the pharmacy. A copy of this record must be returned to the Sponsor or its designee on completion of the Study for accountability purposes. A clinical research associate will periodically review the drug accountability during the Study. At the end of the Study, all unused and expired medication will be retained until disposition of study medication has been made by the Sponsor or its designee.

10. Assessment of Safety

10.1. Definition and Grading Intensity of Adverse Events/Experiences

An adverse event/experience (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. A treatment emergent adverse event is an event that first appears during treatment, which was absent before or which worsens relative to the pre-treatment state.

Adverse events/experiences comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free, and post-treatment periods, or in a reference group receiving drug therapy, are also to be designated as AEs.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

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

All AEs, whether volunteered, elicited, or noted on physical examination, will be recorded throughout the study.

Where possible, the severity of AEs will be categorized Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 [Cancer Therapy Evaluation Program, 2003] or otherwise as follows:

- **MILD (Grade 1)**: experience is minor and does not cause significant discomfort to subject or change in activities of daily living (ADL); subject is aware of symptoms but symptoms are easily tolerated;

- **MODERATE (Grade 2)**: experience is an inconvenience or concern to the subject and causes interference with ADL, but the subject is able to continue with ADL.

- **SEVERE (Grade 3)**: experience significantly interferes with ADL and the subject is incapacitated and/or unable to continue with ADL.

- **LIFE THREATENING (Grade 4)**: experience that, in the view of the Investigator, places the subject at immediate risk of death from the event as it

occurred (i.e., it does not include an event that had it occurred in a more severe form, might have caused death)[5].

By the CTCAE criteria defined above, the Grade 5 category is death.

10.1.1. Stopping Criteria

Close monitoring of the patients during the study will be performed. Any decision to stop the clinical trial will be immediately communicated to all Investigators and to the FDA and competent authorities of any other participating countries as applicable.

Individual patient dosing will be stopped if:

- A patient exhibits a treatment-emergent adverse event of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher and not likely related to the underlying disease.

A patient will be discontinued if they exhibit an:

- Unexplained fever (> 38.5°C) for > 24 hours.

The study will be halted and FDA will be consulted if:

- One or more unexpected drug-related deaths.
- Onset of one or more drug-related cases of:
  - Heart failure (NYHA Class II or greater);
  - Respiratory failure (Type 1 or Type 2);
  - Acute liver failure (associated with an international normalized ratio (INR) of greater than 1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis);
  - Malignant hypertension (i.e., Diastolic blood pressure > 140 mmHg);
  - Nephrotic syndrome which includes protein in the urine (more than 3.5 grams per day) and one or more of the following clinically significant symptoms: low blood protein levels and/or high cholesterol levels and/or high triglyceride levels and/or edema.

10.2. Criteria for Determining Relationship to Drug

Assessment of causality of suspected AEs is based on associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of

[5] per CTCAE Version 4.0 [published 2009 May 28th]

characteristic clinical or pathological phenomena, exclusion of other causes, and absence of alternative explanations. The Investigator will be asked to assess the causal relationship to the Study drug according to the following classifications:

- **Not related:** Time relationship with Study drug administration is nonexistent or other factors, certain or probable, to have been causative.

- **Unlikely:** Time relationship with Study drug administration is doubtful or other factors, certain or probable, to have been causative.

- **Possible:** Time relationship with Study drug administration may exist. Other possible causative factors may exist (e.g., concurrent disease or concomitant medication). Improvements on rechallenge or dose reduction (if performed) may or may not have been seen.

- **Probable:** Time relationship with Study drug administration likely exists. No other possible causative factors may exist (not reasonably explained by the subject's known clinical state or concomitant medication). Improvements on rechallenge or dose reduction (if performed) have occurred. Recurrence of symptoms on rechallenge (if performed) has occurred. A specific laboratory investigation (if performed) has confirmed the relationship.

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

10.3. Adverse Event Reporting

All AEs and SAEs must be reported, whether or not considered attributable to the test product.

Refer to the most current Investigator's Brochure for reference to safety information which lists the adverse reactions expected for the study product and their frequency of occurrence.

Any death is an SAE by definition and must be reported to Pharsafer Associates Ltd.

Whether or not the AE or SAE is expected or unexpected will be assessed by Raptor Pharmacovigilance and Drug Safety (PVDS) according to a pre-specified Safety Monitoring Plan (i.e., the current Investigator Brochure will be used as reference). It is PVDS's responsibility to make this assessment and to generate and distribute/submit any expedited regulatory reports as appropriate, e.g. IND Safety Reports and Suspected Unexpected Serious Adverse Reaction (SUSARs).

Medical judgement will be used for events that may not be immediately life threatening or result in death or hospitalization, but that may jeopardize the subject or may require

intervention to prevent one of the other outcomes listed in the definition above; to determine if the event ought to be reported as a Serious Adverse Event. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

All SAEs must be reported, whether or not considered attributable to the test product, on a separate SAE Report Form. As much information as possible should be supplied at the time of the initial report with at least the following information:

- Subject, treatment, and Study identifiers;
- Investigator's name and address;
- Description of the event, action taken, and outcome;
- Date and time of onset of the event and current status;
- Any suspect (Study or concomitant) drug, with its start date, dose, and form of administration;
- Reason the AE is regarded as serious;
  Current assessment of causality; and
- Any other available diagnostic information that will contribute to the understanding of the event.

The Investigator must report to [redacted] within 24 hours of when the Investigator is aware of the occurrence of the SAE, whether or not the SAE is related to the Study drug. An initial written report should be submitted within 24 hours of the Investigator's awareness of the event, consisting of the SAE report form accompanied by the demographics, medical history, AE, and the concomitant medications pages from the CRF. All pertinent information must be followed by a full written follow-up report to [redacted] within 3 calendar days. As complete a report as possible, (e.g., results of any additional tests) should be forwarded within 8 additional calendar days to [redacted] Any significant new information on the SAE and final outcome must be supplied promptly to [redacted] will notify the Lead Investigator of any significant safety findings arising from all SAE reports.

The SAEs must be reported to the Medical Monitor/Sponsor medical representative:

[redacted]

Investigators will be notified of any SUSAR reports or unanticipated safety concern occurring in other sites conducting studies on RP103. Investigators will notify their local IRB or EC of such reports or safety concerns in accordance with regulatory requirements.

If an Investigator has safety concerns he/she wishes to discuss with the Raptor Medical Monitor he/she should contact the Raptor Medical Monitor.

10.4. Follow-up of Adverse Events and Serious Adverse Events

The reference time point for adverse events is the period from signing the informed consent through the final study visit. Adverse events/experiences will be followed until the event resolves or stabilizes and must be recorded on the AE eCRF. If clinically significant findings are present at the Study termination, a determination will be made about each persistent clinically significant finding. If not clinically important (i.e., does not pose a health risk to the subject) then follow-up will cease. If clinically important, additional follow-up will continue on a case-by-case basis until satisfactory resolution or resolution with sequelae is determined. Any SAE assessed as not related to Study drug will be followed as clinically indicated until its resolution or, if not resolving, until considered stable or until the completion study visit, whichever comes first. Any SAE assessed as related to Study drug will be followed as clinically indicated until its resolution or resolution with sequelae is determined.
Outcome may be classified as resolved, resolved with sequelae, continuing, fatal, or unknown (lost to follow-up).

Pregnancy
If a female subject becomes pregnant during the Study, the Sponsor's Medical Monitor must be notified immediately. Although pregnancy is not considered an SAE, an abnormal outcome of pregnancy may lead to a SAE. Therefore, the SAE Report Form will be used to report the pregnancy of a female Study participant to the Sponsor. Pregnancies must be followed until birth, termination of the pregnancy, or loss of subject follow-up.

11. Statistical Plan

11.1. Statistical Methods

This Study is designed to assess the safety and tolerability of Cysteamine Bitartrate Delayed-release Capsules (RP103) in patients with cystinosis.

A statistical analysis plan will be developed that describes in detail, the statistical methods to be used and will be finalized prior to database lock. This document may modify the plans outlined in the protocol; however, any major modifications of the Study endpoint definitions will be reflected in a protocol amendment.

Demographic and disposition data, drug administration, medical history, prior and concomitant medications, AEs, clinical laboratory measurements, vital signs, ECG measurements and physical examination findings will be summarized. Descriptive summaries of mean and mean changes from screening will be presented for the safety laboratory parameters (hematology, serum chemistry and urinalysis, as applicable),

vital signs and ECGs. The overall incidence of subjects with adverse events will be summarized by System Organ Class (SOC) and Preferred Term (PT) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Summaries by maximum severity, drug –relationship (as determined by the investigator) and drug discontinuation will also be presented. In addition, summaries of annualized exposure adjusted AE rates as well as summaries of the incidence of subjects with AEs by study year of onset (Year 1, Year 2 and Year 3 or later) will be generated. The overall incidence of subjects with serious adverse events (SAEs) will be summarized by SOC and PT. The annualized exposure adjusted SAE rates as well as the incidence by study year will also be tabulated. Safety laboratory values outside reference ranges will be flagged in laboratory listings.

AEs will be categorized using MedDRA, and listed by verbatim, primary term and SOC. SAEs will include MedDRA coding of primary and secondary (non serious) event terms.

[redacted]

Cysteamine concentrations and WBC cystine levels will be summarized per patient.

Pharmacokinetics:
The steady-state plasma concentration profiles of cysteamine will be determined for each patient and the $AUC_{0\text{-}t}$, C_{min}, C_{max}, T_{max} and $t_{½}$ PK parameters will be estimated using non-compartmental methods.

11.2. Analysis Set

All subjects who receive at least 1 dose of Study drug (RP103) will be included in the safety analysis set. All subjects who complete all protocol-specified dosing days (RP103) with evaluable PK, PD data will be included in the PK, PD analysis sets.

11.3. Sample Size Considerations

Sample size is determined by the number of patients who participated in the previous phase III Study (RP103-03) and any additional patients, who did not complete the RP103-03 study, who enroll after all patients that participated in RP103-03 have completed and data have been analyzed.

11.4. Interim Analysis

An interim safety analysis will be performed in time to provide a safety update during the NDA process.

11.5. Accountability Procedure

Missing values will not be imputed.

11.6. Termination Criteria

All ongoing enrolled patients will continue to be dosed until patient withdrawal, or the Investigator withdraws the patient from the Study.

11.7. Deviation Reporting

The following protocol deviations will be recorded and summarized in the final report: 1) eligibility (inclusion/exclusion) violations, 2) study drug dosing violations, 3) excluded medication violations, 4) procedures performed outside the protocol-specified window, 5) procedures not done, 6) subject non-compliance and 7) other, to be specified by the Investigator.

All protocol deviations will be presented in a data listing.

12. Administrative aspects

12.1. Change in Protocol

There will be no alterations in the protocol without prior agreement between the Sponsor's representative, the IRB/EC, and the Investigator. Protocol amendments will be submitted to Regulatory Authorities and to the Investigators for submission and reviewed by IRB/ECs.

12.2. Disclosure

All information provided regarding the Study, as well as all information collected/documented during the course of the Study will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentations, abstracts, etc.) by the Investigator(s) or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

12.3. Monitoring

The Sponsor will designate a Sponsor's Study Monitor (i.e., clinical research associate) who will be responsible for monitoring this clinical trial. The Sponsor's Study Monitor will monitor the Study conduct; insure the proper completion and retention of original source documentation completion and retention, accurate Study drug accountability

records and prompt data entry to eCRF. To this end, the Sponsor's Study Monitor will visit the Study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Sponsor's Study Monitor have access to all documents (related to the Study and the individual participants) at any time these are requested. In turn, the Sponsor's Study Monitor will adhere to all requirements for subject confidentiality as outlined in the Informed consent form (ICF). The Investigator(s) or their representative(s) will be expected to cooperate with the Sponsor's Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information. Investigator(s) or their representative(s) are required to respond in writing to any deficiencies or protocol deviations noted by the monitor in the site visit report.

12.4. Institutional Review Board or Ethics Committee

In accordance with 21 CFR 56, the protocol, advertisement, and Informed Consent Form (ICF) and assents will be reviewed and approved by the IRB or EC. The Sponsor will supply relevant material for the Investigator to submit to the IRB/EC for the protocol's review and approval. Verification of the IRB/EC unconditional approval of the protocol and the written ICF/assent statement will be transmitted to the Investigator.

The IRB/EC will be informed by the Investigator(s) or their representative(s) of subsequent protocol amendments and of serious and unexpected AEs. Approval for protocol amendments will be transmitted in writing to the Investigator. If requested, the Investigator(s) or their representative(s) will permit audits by the IRB/EC, Sponsor Representatives and Regulatory inspections by providing direct access to source data/documents.

The Investigator(s) or their representative(s) will provide the IRB/EC with progress reports at appropriate intervals (not to exceed one year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator(s)' participation in the Study.

12.5. Patient Insurance

If applicable, patient insurance will be secured according to national or local requirements. Where applicable, the name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured will be provided in the Investigator's File.

12.6. Informed Consent and Assent

Written informed assent for the Study will be obtained from all pediatric patients and informed consent will be obtained from their parents or legal guardian before protocol-specific procedures are carried out. For adults above the age of 18 years written informed consent for the Study will be obtained before protocol-specific procedures are carried out. The ICF/assents generated by the Investigator(s) or their

representative(s) will be approved (along with the protocol) by the IRB or EC and will be acceptable to the Sponsor.

The Investigator(s) or their representative(s) will explain the nature of the Study and the action of the test product, and will provide time for subject's questions and answers.

The patient (or parent) will be informed that participation is voluntary and that they can withdraw from the Study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the IRB or EC and will be signed by the subject prior to protocol-specific procedures being performed. The consent process will be completely documented in each subject's source record.

The patient (or parent) will be given a copy of the signed consent/assent, and the originals will be maintained with the patient's records.

12.7. Records

The results from Screening and data collected during the Study will be recorded in the patient's CRF (either paper or electronic CRF). To maintain confidentiality, the patients will be identified only by numbers and/or initials.

If applicable, the completed CRFs will be transferred to the Sponsor or designee and copies of each CRF will be retained by the Investigator. All source documents, records, and reports will be retained by the Study site in accordance with 21 CFR 312.62(c). All primary data, or copies thereof (e.g., laboratory records, CRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the Study and are necessary for the reconstruction and evaluation of any Study report, will be retained in the Study site archives.

12.8. Quality Control and Quality Assurance

Accurate, consistent and reliable data will be ensured through the use of standard practices and procedures. Site initiation visits will be conducted at the clinical site. Experienced clinical research associate(s) (CRAs) will monitor the Study and verify that the data is accurate. Sponsor, or designee, representatives of the FDA or other Regulatory Agencies, including the IRB/EC representatives, may also conduct an audit of the study. Sponsor will contract with a qualified contract research organization(s) (CRO) to perform the data management of this trial. The Medical Monitor, CRAs and site personnel will be trained by the CRO and/or Sponsor. Analysis of samples for plasma cysteamine and WBC cystine will be performed by a central bioanalytical laboratory contracted by Raptor. Drug Safety Reporting will be the responsibility of Sponsor or its representative. System backups for data stored at the CRO, and records retention for the Study data will be consistent with the standard procedures for the CRO.

12.9. Archiving of Data

The Investigator shall arrange for the retention of the patient identification codes for at least 15 years after completion or discontinuation of the Study. Patient files and all original source documents shall be kept for the maximum period of time permitted by the hospital or institution. The Investigator shall retain the trial related essential documents until the Sponsor informs the Investigator these documents are no longer needed.

All data and documents shall be made available at the request of relevant authorities. The Investigator shall inform the Sponsor before any records are destroyed.

12.10. Study Funding

The Sponsor will support the work of the Investigator. All details are fixed in the individual contracts or financial agreements.

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14. Appendices

14.1. Schedule of Events: Main Study (All Subjects)

Procedure	Screening[a]	Dose Confirmation Period		Visit Frequency		End of Study[f]
Study Visit	**Day -28 to -1**	**Day 1[b]**	**Day 4 and Day 5**	**Monthly[d] (± 7 days)**	**Quarterly[e] (± 7 days)**	**7 (± 2) days after last visit, or decision to terminate**
Number of Study Visits	**1**	**1**	**2**	**6 to 9**	**5 to 6**	**1**
Informed Consent	X					
Inclusion/Exclusion	X	X[c]				
Demographics	X[g]					
Medical History	X[g]	X[c]				
Medication History	X[g]	X[c]				
Menstrual Cycle History (females of child-bearing potential only)	X[g]	X[c]				
Serum Pregnancy Test (females with childbearing potential only)	X	X[c]		X	X	
Body height	X	X[c]		X	X	X
Body weight	X	X[c]		X	X	X
BMI calculations	X	X[c]		X	X	X
BSA calculations	X	X[c]		X	X	X
Physical Examination[i]	X[h]	X[c]		X	X	X
Clinical Laboratory Test: Hemotology, Chemistry, Urinalysis[j]	X[h]	X[c]		X	X	X
ECG[k]	X[h]	X[c]		X	X	X
Vital signs[l]	X[h]	X	X	X	X	X
[redacted]	X	X[c]		X	X	X
[redacted]	X	X[c]		X	X	X
Daily diary: training	X					
Daily Diary: medications	X	X		X	X	
Daily Diary: collection		X		X	X	X
Food/liquid intake control[s]		X[c]	X	X	X	X
Q12H RP103 administration[o]	X[h]	X	X	X	X	
WBC Cystine (PD) sample collection[p] collection	X	X[c]	X (post-dose)	X	X	X
Cysteamine (PK) sample collection[q]	X	X	X (post-dose)	X	X	X
Investigator Review of Safety and PK/PD data[r]			X	X	X	
Concomitant medications	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X

a. For patients completing Study RP103-03, Screening can be performed concurrent with the RP103-03 End of Study Visit and will be considered Day -1 for this Study. For patients that did not participate in the RP103-03 study, Screening can take place up to 28 days prior to the first Study visit (Day 1).
b. Day 1 Visit is only to be performed for patients that did not complete Study RP103-03.

c. These procedures were should have been performed at Screening and are to be repeated only if the Day 1 visit occurs more than 7 days after the Screening visit.
d. A minimum of 6 consecutive Monthly (± 1 week) Visits will be conducted for all patients who completed Study RP103-03 prior to enrolling in study RP103-04. Subjects who did not complete Study RP103-03 will not attend Monthly visits.
e. Quarterly visits will take place by the middle of the first month (± 7 days) of each calendar quarter (i.e., January 15, April 15, July 15 and October 15) so that samples can be analyzed on the bioanalytical lab's quarterly analysis schedule.
f. The End of Study visit will be conducted within 7 (± 2 days) from the last completed study visit or from the date of decision to terminate.
g. For patients that completed the RP103-03 Study, data can be obtained from the RP103-03 Screening visit.
h. For patients that completed the RP103-03 Study, data can be obtained from the RP103-03 End of Study Visit.
i. Physical examinations are to include standard physical assessments together with a neurological and skin examination.
j. Clinical laboratory (chemistry and hematology) and urinalysis samples will be collected at Screening (if required) and at Monthly and Quarterly visits, thereafter and at the End of Study (EOS) visit.
k. 12-lead ECG will be collected within 30 minutes prior to Study drug administration at Screening (if required) and at Monthly and Quarterly visits, thereafter and at the End of Study (EOS) visit. For patients that did not complete Study RP103-03, the 12-lead ECG will also be conducted at approximately 3 hours (± 15 minutes) post RP103 dose on Day 1.
l. Vital signs will be measured within 30 minutes prior to Study drug administration at Screening (if required) and at Monthly and Quarterly visits, thereafter and at the End of Study (EOS) visit. For patients that did not complete Study RP103-03, vital signs will also be repeated 30 minutes prior to Study drug administration on Day 1.
m. [redacted]
o. RP103 will be administered Q12H daily. Patients that completed Study RP103-03 will continue to receive their Q12H RP103 dose determined during that Study. For patients that did not complete Study RP103-03, the first dose of RP103 will be given on Day 1, with a starting Q12H RP103 dose at a total daily dose which is 70% of their total daily dose Cystagon® dose.
p. A PD (WBC cystine) sample will be collected at: Screening, (if patient did not complete Study RP103-03) at 5-6 hours after the last Cystagon® dose, on Day 1 (if patient did not complete Study RP103-03) immediately prior (≤ 15 minutes) to morning dose administration of RP103, and for all patients at 0.5 hour (30 minutes) post RP103 dose on Monthly and Quarterly Visits, thereafter and at the End of Study (EOS) visit. For patients who have transitioned back to Cystagon®, the EOS visit PD blood sample will be collected immediately prior to their next Cystagon® dose.
q. A PK (plasma cysteamine) sample will be collected at: Screening (if patient did not complete Study RP103-03) at 5-6 hours after the last Cystagon® dose, on Day 1 (if patient did not complete Study RP103-03) immediately prior (≤ 15 minutes) to morning dose administration of RP103, and for all patients at 0.5 hour (30 minutes) post RP103 dose on Monthly and Quarterly Visits, thereafter and at the End of Study (EOS) visit. For patients who have transitioned back to Cystagon® PK blood sample at the EOS visit will be collected immediately prior to their next Cystagon® dose.
r. Investigator will perform a review of available safety, PK and PD date prior to or at study visits (i.e., Monthly/Quarterly). A dose adjustment may be indicated, as described in Section 8.5. For patients who did not complete Study RP103-03, the first potential dose adjustment should be as soon as the Investigator receives WBC cystine results for the Dose Confirmation Period, so that any RP103 dose adjustment may be implemented before the subject returns for their next study visit (Quarterly Visit 1).
s. Food should try to avoid eating food for at least 2 hours before and 30 minutes after RP103 administration. In case patients cannot comply with this recommendation, they should ingest at least a small amount of food around the time of RP103 dosing (from 1 hour before to 1 hour afterwards).

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14.3. Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975.
35th WMA General Assembly, Venice, Italy, October 1983.
41st WMA General Assembly, Hong Kong, September 1989.
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004.

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the Sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

- The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
- The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]
- At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]
- The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

- In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

1) Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm. All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

2) Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

14.4. Required Elements of Informed Consent

The informed consent discussion, the written informed consent form, and any other written information provided to subjects should include explanations of the following:

A. That the trial involves research.
B. The purpose of the trial.
C. The trial treatments, and the probability for random assignment to each treatment.
D. The trial procedures to be followed, including all invasive procedures.
E. The subject's responsibilities.
F. The experimental aspects of the trial.
G. The reasonably foreseeable risks or inconveniences to the subject.
H. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
I. The alternative procedures or courses of treatment that may be available, and their important potential benefits and risks.
J. The compensation or treatment available to the subject in the event of trial-related injury.
K. The anticipated prorated payment, if any, to the subject for participating in the trial.
L. The anticipated expenses, if any, to the subject for participating in the trial.
M. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
N. That the monitors, auditors, IRB, and regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
O. That the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.
P. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
Q. The person to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
R. The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
S. The expected duration of the subject's participation in the trial.
T. The approximate number of subjects involved in the trial.

14.5. Instructions for Calculating Body Mass Index and Surface Area

- Screening height will be used for all body mass index (BMI) calculations. The formula for calculating BMI is:

$$BMI = weight\ (kg) \div height\ (m)^2$$

Example: The BMI of a subject 1.7 m tall who weighs 90 kg is:

$$BMI = 90 \div 1.7\ m^2 = 31.1\ kg/m^2$$

- To calculate body surface area (m^2) the method of Haycock is being used [Haycock GB, *et al*, 1978]

$$m^2 = [Height\ (cm)^{0.3964} \times Weight\ (kg)^{0.5378}]\ 0.024265$$

Note: 2.2 lb = 1 kg; 1 in = 0.0254 m = 2.54 cm

14.6. Pharmacokinetic Sample Collection and Processing

14.6.1. Collection

Blood samples (approximately 1 mL) for analysis of cysteamine will be collected in chilled (+2°C to +8°C) 1 or 2 mL green-top Vacutainer evacuated collection tubes containing sodium heparin.

Each sample tube should bear the following information on the label:

- RP103-04
- Subject identification number and/or initials
- Nominal time
- Date

After collection, tubes will be mixed by gently by inverting 2 to 3 times and stored in an ice water bath until they are centrifuged (i.e., within 1 hour of collection).

14.6.2. Processing

Blood samples will be centrifuged at 2000g and 4°C for at least 10 minutes. Samples must be processed within 1 hour of collection. The plasma will be split into two approximately equal volumes and placed into CryoTubes and frozen at approximately –70°C or below.

All CryoTubes will be properly labeled and stored at approximately –70°C or below until transfer. Each CryoTube should bear the following information on the label:

- RP103-04
- Subject identification number and/or initials
- Nominal time
- Date
- Tube number of the total number of plastic CryoTubes

1. One of the two aliquots will be shipped to the central bioanalytical laboratory with sufficient dry ice to last the duration of transit. The second aliquot should be shipped separately.

14.7. Pharmacodynamic Sample Collection and Processing

14.7.1. Collection

Blood samples (4 mL) for analysis of WBC cystine will be collected in a 4 mL green-top Vacutainer evacuated collection tubes containing sodium heparin.

Each sample tube should bear the following information on the label:

- RP103-04
- Subject identification number and/or initials
- Nominal time
- Date

After collection, tubes will be mixed by gently by inverting 2 to 3 times and stored at room temperature and should be processed as soon as possible (i.e., within 30-60 minutes of collection).

14.7.2. Processing

The following processing procedure was taken from the University of California, San Diego Cystine Determination Laboratory website.

Refer to the study manual for the actual procedure. A summary of this procedure is provided below. If any discrepancies exist then defer to the study laboratory manual for precise instructions.

2. ACD-Dextran should be at room temperature before using. The 0.9% NaCl, 3.6% NaCl, and distilled water should be placed on ice. Determine the correct setting for your centrifuge from the chart provided in your laboratory manual.
3. Draw 4 mL of heparinized blood (0.1 mL heparin, Na or Li in syringe or a green top vacutainer).
4. As soon as possible transfer blood from vacutainer to the 15 mL centrifuge tube, add an equal volume of ACD-Dextran, cap and invert to mix. Then remove cap or trapped blood may dribble down later. Set on ice for 30-45 minutes.
5. Transfer supernatant to a clean 15 mL centrifuge tube. Centrifuge for 10 minutes at 5° C at your centrifuge setting.
6. Discard supernatant. The white cell pellet will look red.
7. Add 0.8 mL of 0.9% NaCl and 2.4 mL of distilled water. Start timing and vortex continuously at moderate speed for 90 seconds and then add 0.8 mL of 3.6% NaCl. If there is a small red cell clot, remove it. Spin for 3 minutes at 5° C at your centrifuge setting.
8. Discard supernatant and repeat step 6.

9. Add 3.0 mL of 0.9% NaCl. Gently resuspend pellet by vortexing. Pellet does not have to be completely resuspended. Spin for 3 minutes at 5° C at your centrifuge setting.
10. After discarding supernatant, add as accurately as possible, 0.3 mL of distilled water. Re-suspend gently and transfer all of the cell suspension to a clean, labeled, Eppendorf tube. If the pellet is gummy and resists suspension, it may help to cut off the end of a clean blue tip for use in transferring. Transfer EVERYTHING to the Eppendorf tube, even if it remains a glob.
11. Lyse the white cells by freezing in a dry ice/ethanol bath and then place in a warm water bath until just thawed and no longer. Tube may be supported in the bath. Repeat two more times.
12. Wipe off the tube. Immediately transfer all (0.1 mL) of the 12% sulfosalicylic acid (SSA) solution to the Eppendorf containing the lysed cells and vortex. Label with subject identification number and/or initials, date, and nominal time.
13. Freeze sample to -70°C or below. The sample can remain frozen for at least two weeks.

The sample(s) will be sent to the central bioanalytical laboratory with sufficient dry ice to last the duration of transit.

[redacted]

14.9. RP103 DOSING INSTRUCTIONS

14.9.1. RP103 DOSE AND FOOD TIMING

- Subjects should not eat for at least 2 hours before taking and at least 30 minutes after taking RP103.
- Subjects who are unable to take RP103 without eating should eat only a small amount (approximately 4 ounces or ½ cup) of food between 1 hour before and 1 hour after taking RP103.
- Dairy products should be withheld between 1 hour before and 1 hour after taking RP103.

14.9.2. RP103 DOSING IN FOOD

Below are instructions for subjects unable or unwilling to take whole, intact RP103 capsules and prefer to dose in food.

OPTION 1 – EATING:

- Open all the capsules for either the morning or evening dose and sprinkle the contents onto approximately 4 ounces of an acceptable soft food.
- Gently stir the medication beads into the soft food, creating an RP103-food mixture.
- Eat the entire amount of RP103-food mixture. This may be followed by 8 ounces (1 cup) of an acceptable liquid.

OPTION 2 – ADMINISTRATION BY G-TUBE, NG-TUBE OR GJ-TUBE:

- Open all the capsules for either the morning or evening dose and sprinkle the contents onto approximately 4 ounces of applesauce (NOT liquid).
- Gently stir the medication beads into the soft food, creating an RP103-applesauce mixture.
- Place the syringe tip at the bottom of the container of RP103-applesauce mixture; draw up a third of the mixture.
- Keeping the syringe tip at the bottom of the container, mix for a few seconds, then draw up another one-third of the RP103-applesauce mixture. Repeat this step and draw up the final one-third of the RP103-applesauce mixture. This method prevents air from entering the syringe.
- Place syringe on the feeding tube and slowing dispense until the RP103-applesauce mixture is at the end. This removes any air from the tube.
- Place the tube on the button. Deliver the RP103-applesauce mixture at a rate of 10mL/10 seconds, until the syringe is fully dispensed into the tube.
- Take a syringe of acidic juice or other acceptable liquid and deliver through the tube to ensure the entire RP103-applesauce mixture has been administered into the body, and no beads are left in the tube.

* ***The RP103-food/RP103-applesauce mixture must be eaten or administered within 2 hours after preparation.***

14.9.3. **RP103 DOSING IN LIQUID**

Below are instructions for subjects unable or unwilling to take whole, intact RP103 capsules and prefer to dose with liquid.

OPTION 1 – ADMINISTRATION BY ORAL DOSING SYRINGE:

- Open all the capsules for either the morning or evening dose and sprinkle the contents into 4-6 ounces of an acceptable liquid.
- Mix gently for 5 minutes, then draw up the RP103-liquid mixture into a dosing syringe. Administer the entire dose **by mouth**. Do NOT administer the RP103-liquid mixture by G-tube, NG-tube or GJ-tube.
- Eat the entire amount of RP103-food mixture. This may be followed by 8 ounces (1 cup) of an acceptable liquid.

OPTION 2 – DRINKING:

- Open all the capsules for either the morning or evening dose and sprinkle the contents into 4-6 ounces of an acceptable liquid.
- Mix gently for 5 minutes in an uncovered cup, or – shake gently for 5 minutes in a covered cup (e.g., "sippy cup"). Drink all of the RP103-liquid mixture.

* ***The RP103-liquid mixture must be drunk or administered within 30 minutes after preparation.***

14.9.4. **ACCEPTABLE/UNACCEPTABLE FOODS AND LIQUIDS**

Acceptable soft foods for RP103 dosing:
Applesauce (not compote, not chunky), non-dairy pudding, or berry jelly.

Acceptable liquids for RP103 dosing:
Fruit juice, e.g., orange juice (preferred), apple juice or any acidic fruit juice, PolyCitra, PolyCitra-K, non-caffeinated soda (allow bubbles to disperse so that soda is somewhat flat), or bottled or tap water with lemon concentrate added (¼ teaspoon concentrate per ¼ ounce water / 1mL lemon concentrate per 7mL water).

Unacceptable foods and liquids for RP103 dosing:
Milk, dairy products, alcoholic beverages, liquids or foods with a pH from neutral to basic (e.g., bottled or tap water without lemon concentrate added).