CLINICAL PROTOCOL

Protocol No.: **RP103-MITO-002**

Title: A Long-Term Open-Label Extension Study of RP103-MITO-001 to Assess the Safety, Tolerability and Efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103) for Treatment of Children with Inherited Mitochondrial Disease

Phase: 2a

Amendment: 0

Date: **16 December 2014**

Sponsor: Raptor Pharmaceuticals Inc.
7 Hamilton Landing, Suite 100
Novato, CA 94949
United States of America

Lead Investigator: [redacted]

Sponsor Approval:

[redacted]
Acting Medical Director
Raptor Pharmaceuticals Inc.

[redacted] December 16, 2014
[redacted] Signature / Date

1. SYNOPSIS

Protocol Number:	**RP103-MITO-002**
Protocol Title:	An Open-Label Extension Study of RP103-MITO-001 to Assess the Safety, Tolerability and Efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103) for Treatment of Children with Inherited Mitochondrial Disease
Sponsor:	Raptor Pharmaceuticals Inc. 7 Hamilton Landing, Suite 100 Novato, CA 94949 United States of America
Phase:	2a
Indication:	Inherited Mitochondrial Disease
Objectives:	**Primary Objective:** • To assess safety, tolerability and efficacy of long-term repeat dosing of RP103 in patients with inherited mitochondrial disease. **Secondary Objective:** • To assess the steady-state pharmacokinetics (PK) and pharmacodynamics (PD) of RP103. at steady state, in patients with inherited mitochondrial disease.
Study Design:	This is an open-label extension study of RP103-MITO-001 to assess the safety, tolerability and efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103) for treatment of children with inherited mitochondrial disease. Subjects who have completed all visits associated with Study RP103-MITO-001 study will be offered enrollment in this extension study. If enrolled in RP103-MITO-002, subjects will continue to return to the clinic quarterly (every 3 months) for detailed assessments. The Study Exit visit will occur when RP103 is available through the appropriate marketing approval, or a subject withdraws/is withdrawn from the study; or the Sponsor terminates development of RP103 for the treatment of mitochondrial disease. Maximum treatment time in the study is estimated to be 24 months.
Study Visits:	Day 1 (Baseline): is the day of enrollment, and will occur simultaneously with the RP103-MITO-001 Study Exit Visit.

	Quarterly Visits: will begin within 3 months (±7 days) of the RP103-MITO-002 Day 1 Visit and will continue quarterly (every 3 months). Study Exit Visit: will take place upon study completion (i.e. marketing approval has been granted for RP103 and the subject is able to obtain it commercially), study termination, or upon individual subject termination.
Planned Sample Size:	Up to 25 subjects (the maximum number of participants planned for Study RP103-MITO-001).
Number of Sites:	4 sites
Site Location(s):	United States of America
Eligibility Criteria:	Subjects must continue to meet the following eligibility criteria that had been specified in the previous Study RP103-MITO-001): **Inclusion Criteria:** 1. Completed all visits associated with Study RP103-MITO-001. 2. Body weight ≥ 5 kgs. 3. The subject must be willing to abstain from initiating dietary supplements and non-prescribed medications except as allowed by the Investigator, throughout the study (from Day 1 to Study Exit). 4. Willing and able to comply with study drug dosing requirements, i.e. ingest the RP103 capsules intact, or sprinkled in liquid or soft food, or using a G-tube. 5. Sexually active female subjects of childbearing potential (i.e., not surgically sterile [tubal ligation, hysterectomy, or bilateral oophorectomy]) must agree to utilize two of the following acceptable forms of contraception throughout the study (from Day 1 to Study Exit): a) Hormonal contraception: birth control pills, injection, patch, vaginal ring or implant; b) Condom or diaphragm, with spermicide; c) Intrauterine device (IUD); d) Sterile male partner (vasectomy performed at least 6 months prior to the study). 6. Patient's legally authorized representative must provide written informed consent; Patient must provide assent, if required by local/institutional requirements.

	Exclusion Criteria: 1. Documented diagnosis of concurrent inborn errors of metabolism 2. Platelet count, lymphocyte count or hemoglobin below the lower limit of normal at the Day 1 (RP103-MITO-001 Study Exit) Visit. 3. Hepatic insufficiency with liver enzyme tests (alkaline phosphatase, AST or ALT) greater than 2.5 times the upper limit of normal (ULN) at the Day 1 (RP103-MITO-001 Study Exit) Visit. 4. Bilirubin > 1.2 g/dl at the Day 1 (RP103-MITO-001 Study Exit) Visit. 5. Inability to complete the elements of the study, e.g., coma, hemodynamic instability or requiring continuous ventilator support. 6. Malabsorption requiring TPN, chronic diarrhea, bouts of pseudo obstruction. 7. Severe end-organ hypo-perfusion syndrome secondary to cardiac failure resulting in lactic acidosis. 8. Patients with suspected elevated intracranial pressure, pseudotumor cerebri (PTC) and/or papilledema. 9. Severe gastrointestinal disease including gastroparesis. 10. History of drug or alcohol abuse. 11. History of pancreatitis. 12. Participated in an investigational drug trial (except Study RP103-MITO-001) within 30 days or, within 90 days for a biologic, device, or surgical treatment, for inherited mitochondrial diseases prior to the Day 1 (RP103-MITO-001 Study Exit) Visit. 13. Known or suspected hypersensitivity to cysteamine and penicillamine. 14. Female subjects who are nursing, planning a pregnancy, known or suspected to be pregnant, or with a positive serum pregnancy test at the Day 1 (RP103-MITO-001 Study Exit) Visit. 15. Patients who, in the opinion of the Investigator, are not able or willing to comply with the protocol.
Study Drug:	RP103: Cysteamine Bitartrate Delayed-release Capsules (75 mg and 25 mg of cysteamine free-base per capsule)
Route of Administration:	Oral or via G-tube

<table>
<tr><td>Study Drug Dosing Methodology:</td><td>Upon RP103-MITO-002 study entry, subjects will continue on the last total daily dose of RP103 taken during the previous RP103-MITO-001 study. Subsequent RP103 dose adjustments are permitted, e.g., as the subject grows, or if deemed necessary by the Investigator for tolerability reasons.

The Sponsor's medical officer may be consulted for assistance making RP103 dose adjustment decisions at any time during the study.</td></tr>
<tr><td>Study Endpoints:</td><td>Primary Endpoints:
The primary outcome measure will be quality of life based upon the Newcastle Paediatric Mitochondrial Disease Scale (NPMDS)
Secondary Endpoints:
The two preeminent symptoms previously identified during the RP103-MITO-001 study will continue to be assessed in this extension study:
<table>
<tr><th>Symptom</th><th>Measurement Tool(s)</th></tr>
<tr><td>Myopathy</td><td>6-minute walk (6MWT);
Jama dynamometer</td></tr>
<tr><td>Dystonia</td><td>Barry-Albright Dystonia Scale</td></tr>
<tr><td>Ataxia</td><td>Friedreich Ataxia Rating Scale (FARS)</td></tr>
<tr><td>Retarded motor development</td><td>Gross Motor Function Measure (GMFM)</td></tr>
<tr><td>Reduced activities of daily living</td><td>Modified Lansky Play Performance Scale</td></tr>
<tr><td>Vision</td><td>Vision/Eye Examination (LHON subjects)</td></tr>
</table>
Pharmacodynamic Biomarkers: glutathione, glutathione disulfide and lactate
Safety Endpoints:
The safety profile of RP103 will be investigated by changes from the last study visit as noted in the safety assessments: clinical laboratory tests, vital signs, physical examination, 12-lead ECG, seizure activity and incidence of treatment-emergent adverse events.</td></tr>
<tr><td>Safety Assessments:</td><td>The following safety parameters will be evaluated:
Clinical laboratory tests;
Vital signs;
Physical examination;
12-lead ECG;
Seizure activity;
Incidence of adverse events.</td></tr>
</table>

	The active ingredient in RP103 (cysteamine bitartrate) has been associated with CNS symptoms such as seizures, lethargy, somnolence, depression and encephalopathy which are common in this patient population. At each study visit subjects will be queried about the occurrence of potentially cysteamine-associated symptoms since the previous visit using a study-specific Adverse Events Checklist. Safety review of all adverse events will be performed periodically by the Investigator. Particular attention will be paid to potential CNS symptoms reported during the study. The investigator will assess such AEs for relationship to underlying disease versus relationship to study drug, and determine appropriate action(s) to be taken. If the patient has any clinically significant, study drug-related adverse event(s) at the conclusion of the Study Exit Visit, the Investigator will determine if the patient has to be followed further. The subject may be asked to return to the clinic for additional medical tests and examinations to assess resolution of event(s). Outcome may be classified as resolved, resolved with sequelae, continuing, fatal or unknown (lost to follow-up).
Effectiveness Assessments:	The following efficacy parameters will be evaluated: • Change over time as measured at Day 1 (Baseline) and quarterly (every 3 months) and at Study Exit. o Newcastle Paediatric Mitochondrial Disease Scale (NPMDS) • Change over time as measured at Day 1 (Baseline) and quarterly (every 3 months) and Study Exit. o Each subject's two preeminent symptoms from the following: myopathy, dystonia, ataxia, retarded motor development, reduced activities of daily living, vision. o Pharmacodynamic Biomarkers: glutathione, glutathione disulfide and lactate
Duration of the Study:	Up to 2 years (24 months).
Statistical Analyses:	This extension study is designed to assess the efficacy, safety and tolerability of RP103 delayed-release cysteamine bitartrate capsules in patients with inherited mitochondrial disease. The sample size will be up to 25 subjects (the maximum number of participants planned for Study RP103-MITO-001) Any interim analyses will be described in detail in the statistical analysis plan (SAP), which will be developed and specify the statistical methods to be used. The SAP will be finalized prior to

	data cutoff or database lock for the subsequent analysis. Demographic and disposition data, drug administration, medical history, prior and concomitant medications, adverse events, clinical laboratory measurements, vital signs, ECG measurements, physical examination findings, and all other safety data will be listed by subject and timepoint. Descriptive statistics will be tabulated for change and shift from Baseline in the safety laboratory variables (chemistry, hematology, urinalysis), vital signs and ECGs. Adverse events will be summarized by method of collection type, frequency, severity, relationship to study drug, any change in study drug administration, and number of subjects per treatment. Adverse events will be categorized using MedDRA, and listed by verbatim, primary term and system organ class (SOC).

2. SCHEDULE OF EVENTS

PROCEDURE	Baseline Day 1	Quarterly Visits Every 3 Months	Study Exit
Allowable Visit Window	*None*	*+/- 7 days*	*+/- 7 days*
Informed Consent	X		
Assess/Confirm Eligibility	X		
Enrollment	X		
Medical and Medication Histories	X		
Monitoring of Adverse Events	X	X	X
Adverse Events Checklist	X	X	X
Review of Concomitant Meds	X	X	X
Vital Signs[a] (including body temperature)	X	X	X
Height, Weight, Head Circumference[a]	X	X	X
BMI / BSA Calculations[a]	X	X	X
12-lead ECG[a]	X	X	X
Physical Examination[a]	X	X	X
Clinical Laboratory Tests[a, b]	X	X	X
Serum Pregnancy Test[a] (if applicable)	X	X	X
Breath Samples for Hydrogen Sulfide[a]	X	X	X
PD Biomarker Sample Collection[b, c]	X	X	X
PK Sample Collection[c]	X	X	X
Record Seizure Activity[d]	X	X	X
Subject Diary Training/Dispense	X	X	
Subject Diary Collect/Review/Sign	X	X	X
RP103 Administration	X	X	X
Dispense and/or Collect RP103[e]	X	X	X
Administer age-specific NPMDS	X	X	X
Conduct two of the following assessments, already specified during participation in previous Study RP103-MITO-001:			
6-minute Walk Test ; Jama Dynamometer	X	X	X
Barry-Albright Dystonia Scale	X	X	X
Friedreich Ataxia Rating Scale	X	X	X
Modified Lansky Play Performance Scale	X	X	X
Gross Motor Function Measure	X	X	X
Vision/Eye Examination	X	X	X

Schedule of Events Footnotes

a RP103-MITO-001 Study Exit is to take place on the same day as RP103-MITO-002 Day 1 (Baseline). Data collected from the RP103-MITO-001 study (i.e. medical history, ongoing adverse events, concomitant medications, Study Exit vital signs) may be carried forward to the extension study clinical database. Data recording and entry instructions will be supplied via the electronic CRF instructions.

b Clinical Laboratory Tests and PD Biomarkers are specified in Protocol Table 2;
Samples for Clinical Laboratory Tests and PD Biomarkers should be collected at the same time as PK blood samples.

c PK blood samples will be collected within 30 minutes before or after the RP103 morning dose.

d Seizure activity may be recorded by patients/caregivers using a paper seizure diary handed out by the site, or the form provided on www.seizuretracker.com website. If patients use the web-based form, it must be printed out and used as source documentation for any associated CRF data entry.

e RP103 from the previous Study RP103-MITO-001 must be taken for the morning dose and associated PK blood draws on the day of Study Exit. Then, RP103 for Study RP103-MITO-002 is to be dispensed for the evening dose (RP103-MITO-002 Day 1) and to be taken every 12 hours for the remainder of participation in Study RP103-MITO-002.

3. INVESTIGATOR SIGNATURE PAGE

Investigator Statement

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)

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
8-OHdG	8-hydroxy-2′-deoxyguanosine
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase (Serum Glutamic Pyruvic Transaminase)
AOPP	Advanced oxidation protein products
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
ATP	Adenosine-5'-triphosphate
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BSA	Body surface area
C	Celsius
CFR	Code of Federal Regulations
CoQ_{10}	Coenzyme Q_{10}
COX	Cytochrome oxidase
CRA	Clinical research associate
CRF	Case report form
CrM	Creatinine monohydrate
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End of Study
EU	European Union
FARS	Friedreich Ataxia Rating Scale
FDA	Food and Drug Administration
FRAP	Ferric reducing antioxidant power
FRDA	Friedreich's ataxia
g	Gram
GMFM	Gross Motor Function Measure
GSH	Glutathione
GSSG	Glutathione disulfide
HbA1c	Hemoglobin A1c
HD	Huntington's Disease
HIPAA	Health Information Portability and Accountability Act of 1996
h	Hour
HPLC	High pressure liquid chromatography
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International normalized ratio
IRB	Institutional Review Board

Abbreviation or Term	Definition/Explanation
IUD	Intrauterine device
Kg	Kilogram
L	Liter
LHON	Leber's Hereditary Optic Neuropathy
LLN	Lower limit of normal
µg	Microgram
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
MERRF	Myoclonus epilepsy with ragged red fibers
MNGIE	Mitochondrial neurogastrointestinal encephalopathy syndrome
Mg	Milligram
Min	Minute
mL	Milliliter
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MTD	Maximum tolerated dose
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NDA	New Drug Application
NIH	National Institute of Health
NPMDS	Newcastle Paediatric Mitochondrial Disease Scale
NYHA	New York Heart Association
OTC	Over the counter
Q6H	Every 6 hours
Q12H	Every 12 hours
QoL	Quality of Life
PD	Pharmacodynamic
PE	Physical examination
PI	Principal Investigator
PK	Pharmacokinetic
P.O.	Per os
POLIP	Polyneuropathy, ophthalmoplegia, leukoencephalopathy, and intestinal pseudo-obstruction
PT	Prothrombin time
RBC	Red blood cell
RC	Respiratory chain
ROS	Reactive oxygen species
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
SI	Small Intestine

Abbreviation or Term	Definition/Explanation
TGa	Tranglutaminase
UCSD	University of California San Diego
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO-DRL	World Health Organization-Drug Reference List

5. INTRODUCTION

5.1. 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).

5.2. Background

Inherited mitochondrial diseases are the majority of mitochondrial diseases (or called mitochondrial cytopathies), a collection (> 40) of energy metabolism disorders. They are the result of defects in mitochondrial DNA (for maternal inheritance) or nuclear DNA (for autosomal inheritance) coding for electron transport chain proteins or other molecules needed for mitochondrial function. Their clinical manifestations are extremely diverse and to various degrees of severity, and often involving multiple different tissues, particularly in cells where require high energy such as brain and muscles. Despite their distinct clinical pictures, mitochondrial diseases share a common feature that mitochondria's ability to produce energy is damaged and consequently the mitochondria is further damaged due to subsequent byproducts accumulation and interference with other chemical reactions in the cells. They are estimated to have a prevalence of 1:5000 to 1:10,000; with approximately 1,000 to 4,000 children born with them in the United States each year. The age of onset varies from early infancy to adulthood, and typically by age of ten, approximately one in 4,000 American children is diagnosed. Available therapies remain supportive and none is effective in curing.[1]

RP103 (whose commercial name is PROCYSBI® (cysteamine bitartrate) delayed-release capsules) are enteric-coated beads of cysteamine bitartrate that are further encapsulated and intended to be administered every 12 hours (Q12H). Cystagon® (cysteamine bitartrate, immediate release, administered every 6 hours, Q6H) was approved for treatment of nephropathic cystinosis in children and adults in the United States (US) on August 15, 1994 by the Food and Drug Administration (FDA) (New Drug Application (NDA) #20-392, Mylan Pharmaceuticals, Inc.) and in the European Union (EU) by the European Medicines Agency (EMA) on June 23, 1997 (MAA by Orphan Europe S.A.R.L). In March 2012, Raptor submitted a NDA to the FDA and a Marketing Authorization Application (MAA) to the EMA for RP103 for the treatment of cystinosis. On April 30, 2013 PROCYSBI (the marketed name for RP103) was approved by FDA in the US for the management of nephropathic cystinosis in adults and children 6 years and older (NDA 203-389). As stated in the PROCYSBI Package Insert, the risks and benefits of treatment with PROCYSBI in children under 6 years old are not yet established (although immediate-release cysteamine bitartrate, Cystagon has been used in children as soon as they are diagnosed, i.e. generally between 12 and 18 months old). As of July 2013, 13 patients between the age of 2 and 6 years old have been enrolled in an extension study and treated for at least one and a half years with Q12H PROCYSBI. Analysis of data is going to be provided to the FDA. On September 6, 2013 EMA approved the

Marketing Authorization Application (MAA) in the European Union (EU) for RP103. Due to the very short half-life of cysteamine, RP103 is the only Q12H formulation of cysteamine that can provide a minimal exposure of cysteamine to blood and tissues.[2]

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 (PROCYSBI Package Insert).

Using a silicone rubber nasoenteric tube, R. Dohil was able to show that, in patients with cystinosis as well as in healthy volunteers, cysteamine oral bioavailability was significantly greater when delivered directly at the level of the proximal small intestine (SI) comparatively to the stomach or the cecum.[3] A rationale (in rats) for this greater SI bioavailability was published only recently though,[4] but confirmed transporter studies done with RP103: cysteamine is transported by organic cation transporters (OCT-1 and OCT-3 in rats, OCT-2 in human cells); these transporters are at especially high density in the intestinal tube where there is a higher level of iron, i.e. the SI. Additionally, cysteamine has been shown to bind to cysteine, which facilitates transfer through the lysosome membrane, the intestinal barrier or the blood brain barrier by the lysine transporter[5,6] or a lysine-like transporter, the PQLC2 protein.[7]

Using a delayed-release formulation (i.e., EC-cysteamine, enteric-coated Cystagon capsules) R. Dohil demonstrated that, due to this greater SI bioavailability, EC-cysteamine resulted in patients maintaining low plasma WBC cystine levels while taking a reduced total daily dose of cysteamine. In 85% of patients treated (six of the seven patients), the total daily dose was reduced.[8] The mean total daily dose of EC-cysteamine was 62% of the previous mean total daily dose of Cystagon. In addition, compared to the study period with Cystagon which required dosing Q6H, the EC-cysteamine was taken only Q12H, eliminating the problem of disrupting sleep with a Q6H dosing schedule while still maintaining adequate reduction of WBC cystine levels.

Based on these preliminary results, Raptor conducted a pilot Phase 2b study, Study RP103-01, to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of RP103 compared to a single dose of Cystagon in 9 patients with cystinosis. Study RP103-01 confirmed that RP103 behaved similar to EC-cysteamine, enteric-coated Cystagon capsules, and therefore, a confirmatory Phase 3 study (RP103-03) was subsequently conducted to determine the efficacy and safety of RP103 compared to Cystagon in patients with nephropathic cystinosis. Study RP103-03 demonstrated that RP103 was non-inferior to Cystagon in maintaining patient WBC cystine levels. Based on results of Study RP103-03, patients were allowed to enroll in Study RP103-04, a long-term safety follow-on study.

For the treatment of cystinosis, the target maintenance dose of PROCYSBI is 1.30 grams/m^2/day administered in two divided doses (one dose every 12 hours (Q12H)). The PROCYSBI dose can be increased to a maximum of 1.95 grams/m^2/day. The dose of 1.95 grams/m^2/day has been associated with an increased rate of withdrawal from treatment with immediate-release cysteamine due to intolerance and an increased incidence of adverse events.

The treatment of inherited mitochondrial diseases with cysteamine is potentially based on different mechanisms of action than that for treatment of cystinosis, although one key biochemical reaction, which is the basis for the treatment of cystinosis, seems to play a significant role also. Cysteamine is an aminothiol that participates in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide. This cysteine-cysteamine mixed disulfide can exit the lysosome through the lysosome membrane,[9] as it is transported through the intestinal barrier or the blood brain barrier, by the lysine transporter[5,6] or a lysine-like transporter, the PQLC2 protein.[7] This biochemical reaction results in an increase of the cellular thiol pool, making more cysteine available for glutathione (GSH) synthesis.[10] Glutathione is composed of the amino acids cysteine, glutamate and glycine.[10] The availability of cysteine, which exists primarily as cystine, is the major rate-limiting factor in GSH production.

Other potential mechanisms of action are probably very similar to those supporting the use of cysteamine for treatment of Huntington's disease (HD). Cysteamine has been tested in patients with HD as early as 1986. At that time, cysteamine was thought to decrease brain somatostatin levels, leading to various behavioral effects that ameliorated the disease phenotype.[11] Subsequently, several potential mechanisms of action have been suggested: inhibition of tranglutaminase (TGa),[12-14] increase of Brain Derived Neurotrophic Factor (BDNF),[15] as well as other mechanisms.[16,17] Cysteamine directly scavenges reactive oxygen species (ROS) including superoxide free radicles, aldehydes (toxic products of lipid peroxidation) and it is one of the few biomolecules that will scavenge hydrogen peroxide.[18,19] In addition, an in-vitro study of brain cortex in young rats showed that cysteamine decreased lipoperoxidation and increased glutathione peroxidase activity (enzyme that metabolizes H_2O_2).[18]

Treatment with RP103 should be progressively initiated. This dose titration has been associated with lower rates of nausea.

5.3. Risk/Benefits

Cysteamine is an aminothiol that drives a disulfide exchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide.

PROCYSBI is approved for the management of nephropathic cystinosis in children and adults. PROCYSBI is contraindicated in patients who have developed hypersensitivity to it or to cysteamine or penicillamine (PROCYSBI Package Insert). Most commonly reported adverse reactions (≥5%) are vomiting, abdominal pain/discomfort, headaches, nausea, diarrhea, anorexia/decreased appetite, breath odor, fatigue, dizziness, skin odor, and rash (PROCYSBI Package Insert). 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 (PROCYSBI Package Insert).

RP103, Cysteamine Bitartrate Delayed-release Capsules, was designed to be a delayed-release product of cysteamine bitartrate which would avoid some of the unwanted side

effects of the compound and extend the duration of effective treatment in a Q12H dosing regimen, thereby helping to improve compliance over the current Q6H round the clock dosing required for immediate release formulation Cystagon effectiveness. Clinical studies have demonstrated that patients with cystinosis are able to maintain a plasma WBC cystine level in the target range equal to or below 1.0 nmol ½cystine/mg protein using a Q12H delayed-release formulation (EC-cysteamine[8] or RP103).

A review of the literature, post-marketing experience of Cystagon since 1994 by the FDA and 1997 by the EMA, the UCSD experience with EC-cysteamine, and Raptor's studies in healthy volunteers, cystinosis patients, [redacted] and H[redacted] with RP103, does not reveal any additional risks to human subjects than what is described in the PROCYSBI Package Insert.

5.4. Study Rationale

On April 30, 2013 PROCYSBI (the marketed name for RP103) was approved by FDA in the US for the management of nephropathic cystinosis in adults and children 6 years and older (NDA 203-389). Raptor is developing this delayed-release formulation with extended-release properties of cysteamine bitartrate (RP103) [redacted]

A recent study in a cohort of children with biochemically and/or genetically confirmed mitochondrial diseases found that their plasma thiols and their redox state are altered, indicating an increase in oxidative stress and depletion of antioxidant supplies.[1] The ability of cysteamine to increase cellular thiol pool can potentially address the relative thiol deficiency in those patients and likely to address the underlying pathophysiology of the diseases. In addition, oxidative stress has been implicated in the pathogenesis of complications of mitochondrial diseases,[1] the ability of cysteamine to directly scavenge reactive oxygen species (ROS) will likely further counterbalance the increased oxidative stress and improve the compromised mitochondria functions and lead to potential treatment effect. Moreover, in a recent publication about a new compound, EPI-743, that seems to have some efficacy in Leigh syndrome,[20] the authors concluded that data support glutathione as a "redox blood signature" in mitochondrial disorders and its use as a clinical trial endpoint in the development of mitochondrial disease therapies.[21]

Cysteamine is an aminothiol that participates in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide. This cysteine-cysteamine mixed disulfide can exit the lysosome through the lysosome membrane,[9] as it is transported through the intestinal barrier or the blood brain barrier, by the lysine transporter[5,6] or a lysine-like transporter, the PQLC2 protein.[7] This mechanism is the rationale that has been successfully used to treat patients with cystinosis for more than 20 years. This biochemical reaction results in an increase of the cellular thiol pool, making more cysteine available for glutathione (GSH) synthesis.[10] Glutathione is composed of the amino acids cysteine, glutamate and glycine.[10] The availability of cysteine, which exists primarily as cystine, is the major rate-limiting factor in GSH production.[22] Recent findings by Mancuso *et al.* reinforce the notions that in mitochondrial diseases oxidative stress is important and can be reduced by administration of a cysteine donor.[23]

Moreover, cysteamine is almost exclusively metabolized in hypotaurine then taurine, and taurine deficiency appears to diminish the formation of 5-taurinomethyluridine and causes inefficient decoding for the mitochondrial codons of leucine, lysine, glutamate and glutamine. The resulting reduction in the biosynthesis of mitochondria-encoded proteins deprives the respiratory chain of subunits required for the assembly of respiratory chain complexes. Hence, taurine deficiency is associated with a reduction in oxygen consumption, an elevation in glycolysis and lactate production and a decline in ATP production. A similar sequence of events takes place in mitochondrial diseases MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) and MERRF (myoclonic epilepsy and ragged-red fiber syndrome). In both diseases, mutations in their respective tRNAs interfere with the formation of 5-taurinomethyluridine in the wobble position. Hence, the taurine-deficient phenotype resembles the phenotypes of MELAS and MERRF.[24]

5.5. Dose Rationale

RP103 will be administered at the same doses and following a progressive dose titration as used in patients with cystinosis for ~ 20 years, since this has been associated with better tolerability.

5.6. Study Conduct

This study will be conducted in compliance with the protocol approved by the local Institutional Review Boards (IRB) or Ethics Committees (EC), and according to FDA and ICH Good Clinical Practice guidelines.

5.7. Study Population

Subjects who have completed all visits associated with Study RP103-MITO-001 and meet the inclusion and exclusion criteria for RP103-MITO-002 (specified in Section 8.1 and 8.2) will be offered enrollment in this extension study.

Patients with inherited mitochondrial diseases associated with nuclear or mitochondrial DNA mutations that impair the respiratory chain. These include, but are not limited to the following clinical syndromes: Leber's hereditary optic neuropathy; myoclonic epilepsy and ragged-red fibers (MERFF); mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS); Kearn-Sayre syndrome; subacute necrotizing encephalopathy (Leigh Syndrome); POLG-related disorders (Alpers-Huttenlocher Syndrome, Autosomal Dominant Progressive External Ophthalmoplegia, Autosomal Recessive Progressive External Ophthalmoplegia, Childhood Myocerebrohepatopathy Spectrum Disorders, Myoclonic Epilepsy Myopathy Sensory Ataxia, POLG-Related Ataxia Neuropathy Spectrum Disorders); Mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE), also called myoneurogastrointestinal encephalopathy syndrome or POLIP syndrome; others, e.g., mitochondrial cardiomyopathies and other syndromes due to multiple mitochondrial DNA deletions.

Up to 25 subjects will be enrolled (the maximum number of participants planned for Study RP103-MITO-001).

6. STUDY OBJECTIVES AND ENDPOINTS

The objective of this study is to assess safety, tolerability and efficacy of RP103 in patients with inherited mitochondrial disease.

6.1. Primary Objective

To assess safety, tolerability and efficacy of long-term repeat dosing of RP103 in children with inherited mitochondrial disease.

6.2. Secondary Objective

To assess the steady-state pharmacokinetics (PK) and pharmacodynamics (PD) of RP103 at steady state, in children with inherited mitochondrial disease.

6.3. Study Endpoints

6.3.1. Primary Endpoints

The primary outcome measure will be quality of life based upon the Newcastle Paediatric Mitochondrial Disease Scale (NPMDS)

6.3.2. Secondary Endpoints

- The two preeminent symptoms previously identified during the RP103-MITO-001 study will continue to be assessed in this extension study:

Symptom	Measurement Tool(s)
Myopathy	6-minute walk (6MWT); Jama dynamometer
Dystonia	Barry-Albright Dystonia Scale
Ataxia	Friedreich Ataxia Rating Scale (FARS)
Retarded motor development	Gross Motor Function Measure (GMFM)
Reduced activities of daily living	Modified Lansky Play Performance Scale
Vision	Vision/Eye Examination (LHON subjects)

- Pharmacodynamic Biomarkers: glutathione, glutathione disulfide and lactate

7. OVERALL STUDY DESIGN AND PLAN

7.1. Study Design

This is an open-label extension study of RP103-MITO-001 to assess the safety, tolerability and efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103) for treatment of children with inherited mitochondrial disease.

Subjects who have completed all visits associated withStudy RP103-MITO-001 will be offered enrollment in this extension study. If enrolled in RP103-MITO-002, subjects will return to the clinic quarterly (every 3 months) for detailed assessments.

7.2. Study Visits

Study visits will occur as follows:

Day 1 (Baseline): is the day of enrollment, and will occur simultaneously with the RP103-MITO-001 Study Exit Visit.

Quarterly Visits: will begin within 3 months (±7 days) of the RP103-MITO-002 Day 1 Visit and will continue quarterly (every 3 months).

- Study Exit Visit: will take place upon study completion (i.e. marketing approval has been granted for RP103 and the subject is able to obtain in commercially), study termination, or upon individual subject termination

7.3. Study Drug Dosing Methodology

Upon RP103-MITO-002 study entry, subjects will continue on the last total daily dose of RP103 taken during the previous RP103-MITO-001 study. Subsequent RP103 dose adjustments are permitted (e.g. as the subject grows, or if deemed necessary by the Investigator for tolerability reasons).

The Sponsor's medical officer may be consulted for assistance making RP103 dose adjustment decisions at any time during the study.NOTE: For each subject, when calculating the number of capsules to be taken every 12 hours (i.e. half of the prescribed total daily dose), if rounding is required to get a whole number of capsules to be taken, then rounding should be down and not up.

7.4. Randomization

Subjects will not be randomized.

7.5. Duration

Study duration is up to 24 months.

8. SELECTION OF SUBJECTS

Subjects must continue to meet the following eligibility criteria that had been specified in the previous Study RP103-MITO-001:

8.1. Inclusion Criteria

1. Completed all study visits associated with Study RP103-MITO-001.
2. Body weight ≥ 5 kgs.
3. The subject must be willing to abstain from initiating dietary supplements and non-prescribed medications except as allowed by the Investigator, throughout the study (from Day 1 to Study Exit).

4. Willing and able to comply with study drug dosing requirements, i.e. ingest the RP103 capsules intact, or sprinkled in liquid or soft food, or using a G-tube.
5. Sexually active female subjects of childbearing potential (i.e., not surgically sterile [tubal ligation, hysterectomy, or bilateral oophorectomy]) must agree to utilize two of the following acceptable forms of contraception throughout the study (from Day 1 to Study Exit):
    a) Hormonal contraception: birth control pills, injection, patch, vaginal ring or implant;
    b) Condom or diaphragm, with spermicide;
    c) Intrauterine device (IUD)
    d) Sterile male partner (vasectomy performed at least 6 months prior to the study).
6. Patient's legally authorized representative must provide written informed consent; Patient must provide assent, if required by local/institutional requirements.

8.2. Exclusion Criteria

1. Documented diagnosis of concurrent inborn errors of metabolism
2. Platelet count, lymphocyte count or hemoglobin below the lower limit of normal (LLN) at the Day 1 (RP103-MITO-001 Study Exit) Visit.
3. Hepatic insufficiency with liver enzyme tests (alkaline phosphatase, AST or ALT) greater than 2.5 times the upper limit of normal (ULN) at the Day 1 (RP103-MITO-001 Study Exit) Visit.
4. Bilirubin > 1.2 g/dl at the Day 1 (RP103-MITO-001 Study Exit) Visit.
5. Inability to complete the elements of the study, e.g., coma, hemodynamic instability or requiring continuous ventilator support.
6. Malabsorption requiring TPN, chronic diarrhea, bouts of pseudo obstruction.
7. Severe end-organ hypo-perfusion syndrome secondary to cardiac failure resulting in lactic acidosis.
8. Patients with suspected elevated intracranial pressure, pseudotumor cerebri (PTC) and/or papilledema.
9. Severe gastrointestinal disease including gastroparesis.
10. History of drug or alcohol abuse.
11. History of pancreatitis.
12. Participated in an investigational drug trial (except Study RP103-MITO-001) within 30 days or, within 90 days for a biologic, device, or surgical treatment, for inherited mitochondrial diseases prior to the Day 1 (RP103-MITO-001 Study Exit) Visit.
13. Known or suspected hypersensitivity to cysteamine and penicillamine.
14. Female subjects who are nursing, planning a pregnancy, known or suspected to be pregnant, or with a positive serum pregnancy test at the Baseline visit.

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

8.3. 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 withdraw a subject from the study if, in the Investigator's opinion, it is not in their best interest to continue participation. Notification of early termination will immediately be made to the Sponsor's representative(s).

In case of early termination, the subject must return to the clinic for a Study Exit visit within 4 weeks after last dosing (28 days +/- 7 days) and perform all assessments detailed in the Schedule of Events (Section 2). The reason for discontinuation will be recorded in source documentation and the eCRF.

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

- Adverse event(s);
- Pregnancy;
- Withdrawal of consent;
- Subject non-compliance;
- Investigator decision;
- Sponsor decision, i.e., cancellation of drug development;
- Request from regulatory agency (e.g., FDA), Institutional Review Board, or Ethics Committee.

9. TREATMENT OF SUBJECTS

9.1. Study Treatment

Raptor Pharmaceuticals Inc. will provide the Investigator with adequate quantities of RP103 (see **Table 1**). The active ingredient in RP103 is cysteamine bitartrate; dosage in its formulation is expressed as mg of cysteamine free base.

Table 1: Study Drug

Study Drug	Cysteamine Bitartrate Delayed-release Capsules (RP103)
Form[a]	Capsules
Strength[b]	25 mg and 75 mg
Supplier	Raptor Pharmaceuticals Inc.
[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.

9.2. Identity of Investigational Product

The 25 mg strength Cysteamine Bitartrate Delayed-release Capsules (RP103, test product) are a size 3 two-toned blue hard gelatin capsules or light blue single tone hard gelatin capsules imprinted with "Raptor/103" or "Raptor" logo and "25 mg" in white ink. They are provided in 60-count bottles.

The 75 mg strength Cysteamine Bitartrate Delayed-release Capsules (RP103, test product) are a size 0 blue two-toned hard gelatin capsules imprinted with "Raptor/103" or "Raptor" logo and "75 mg" in white ink. They are provided in 150-count bottles.

9.3. Storage of Investigational Products

Cysteamine Bitartrate Delayed-release Capsules (RP103) should be stored at controlled room temperature (maintained at 20-25°C, mean temperature not more than 25°C, with excursions permitted from 15 to 30°C), protected from light and moisture. The product must be kept in the original bottle and should not be dispensed into another container. Do not remove the oxygen absorber and desiccant.

9.4. 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 after study entry must also be recorded. Patients must observe the restrictions listed here for the specified time periods and throughout the study.

At the Baseline visit, the patient or parent will be provided with a diary to record protocol specified medications and information (e.g., missed school days, seizure activity) and instructed on its completion. At each study visit, the Investigator staff will review the diary for completeness, errors/corrections and dosing compliance. Staff will issue a new diary for use until the next study visit. 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.

9.5. Study Treatment Administration and Compliance

Upon RP103-MITO-002 study entry, subjects will continue on the last total daily dose of RP103 taken during the RP103-MITO-001 study. Study drug labeled for the previous Study RP103-MITO-001 must be taken for the morning dose and associated PK blood draws on the day of Study Exit (which is also RP103-MITO-002 Day 1). Then, study drug labeled for Study RP103-MITO-002 is to be dispensed for the evening dose (RP103-MITO-002 Day 1) and - to be taken every 12 hours for the remainder of participation in Study RP103-MITO-002.

Detailed instructions for dosing are provided in Section 15.4 and subjects will also be provided with a handout with those same instructions. RP103 administered during study visits will be under the supervision of Investigator personnel.

A daily diary of protocol-specified medications will be maintained throughout the study and will be used to assess RP103 dosing compliance.

10. STUDY PROCEDURES

10.1. Schedule of Study Procedures

Before any study-specific procedures are performed, the patient and legally authorized representative (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.

10.1.1. Day 1 (Baseline) Visit Procedures

- Obtain written consent, and assent if applicable
- Review data collected at the RP103-MITO-001 Study Exit Visit and review/confirm subject meets eligibility criteria for this extension study. If so, proceed with enrollment.
- The following study procedures can be carried forward from the RP103-MITO-001 Study Exit Visit and do not need to be duplicated:
    - Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature).
    - Measure height, body weight and head circumference; calculate BMI and BSA.
    - Perform physical examination.
    - Obtain a 12-lead ECG.
    - Administer age-specific NPMDS (only if not administered during RP103-MITO-001 Exit visit)
    - For each subject, perform the assessments associated with their preeminent symptoms already specified during Study RP103-MITO-001 (and detailed in Section 6.3.2 Secondary Endpoints).
    - Collect blood samples for laboratory tests, within 30 minutes before/after RP103 dose
    - Collect breath samples for hydrogen sulfide testing.
    - Collect and review seizure activity since the previous clinic visit. Dispense a paper seizure diary if applicable (or print from www.seizuretracker.com website).
- For females, re-assess childbearing potential and menstrual history.
- The final dose of study drug labeled for the RP103-MITO-001 should have been taken that morning. Administer study drug labeled for RP103-MITO-002, with instructions to subject to take first dose of study drug for RP103-MITO-002 12 hours later than evening.Dispense RP103 for home administration. Explain and provide the subject and/or caregivers with RP103 Dosing Instructions.
- Provide subject and/or caregivers with re-training on the medications diary; dispense a blank diary for subjects to complete until the next study visit.
- Schedule or confirm the next study visit.

10.1.2. **Quarterly Visit Procedures**

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature).
- Measure height, body weight and head circumference; calculate BMI and BSA.
- For females, re-assess childbearing potential and menstrual history.
- Perform physical examination.
- Obtain a 12-lead ECG.
- Review concomitant medications, documenting any changes since the previous study visit. Medications prescribed on a prn (as needed) basis should be recorded in the eCRF only if actually taken during the study, with defined start and stop dates of dosing.
- Record adverse events experienced, or changes to those already reported, since the previous study visit. Complete the Adverse Events Checklist (Section 15.5)
- Perform the assessments associated with each subject's two preeminent symptoms. (These assessments are specified in the Schedule of Events and Section 6.3.2 Secondary Endpoints).
- Determine subject's current RP103 dose. Administer RP103 dose according to the instructions provided in Section 15.4
- Collect empty and partially empty bottles of RP103. Dispense more RP103 for home administration. Remind the subject and/or caregivers of RP103 dosing instructions.
- Collect blood samples for laboratory tests, within 30 minutes before/after RP103 dose
- Collect breath samples for hydrogen sulfide testing.
- Administer age-specific NPMDS
- Collect (or print from www.seizuretracker.com website) and review seizure activity since the previous clinic visit. Dispense a new paper seizure diary if applicable.
- Collect and review the completed IP diary with the subject and/or caregivers, making corrections as needed. Investigator staff and the subject/caregiver will sign/date the diary as indication of its review and accuracy; dispense a blank diary for subjects to complete until the next study visit.
- Schedule or confirm the next study visit.

10.1.3. **Study Exit Visit Procedures**

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature).
- Measure height, body weight and head circumference; calculate BMI and BSA.
- For females, re-assess childbearing potential and menstrual history.
- Perform physical examination.
- Obtain a 12-lead ECG.
- Review concomitant medications, documenting any changes since the previous study visit. Medications prescribed on a prn (as needed) basis should be recorded in the

eCRF only if actually taken during the study, with defined start and stop dates of dosing.

- Record adverse events experienced, or changes to those already reported, since the previous study visit. Complete the Adverse Events Checklist (Section 15.5)
- Administer age-specific NPMDS
- Perform the assessments associated with each subject's two preeminent symptoms. (These assessments are specified in the Schedule of Events and Section 6.3.2 Secondary Endpoints).
- Determine subject's current RP103 dose. Administer RP103 dose according to the instructions provided in Section 15.4
- Collected empty and partially empty bottles of RP103.
- Collect blood samples for laboratory tests, within 30 minutes before/after RP103 dose
- Collect breath samples for hydrogen sulfide testing.
- Collect and review seizure activity since the previous clinic visit.
- Collect and review the completed diary with the subject and/or caregivers, making corrections as needed. Investigator staff and the subject/caregiver will sign/date the diary as indication of its review and accuracy; dispense a blank diary for subjects.

10.2. Fasting, Diet, Fluid and Activity Control

RP103 will be administered with an acceptable food or liquid and according to the instructions provided in Section 15.4.

10.3. Contraception and Hormone Therapy

10.3.1. Women

If the patient is a female, she will be asked about her menstrual cycle history (including date of last period; menses regularity; typical duration and normalcy; any abnormal discharges; and excessive bleeding).

If she is of childbearing potential and is sexually active, she must be non-lactating and have a negative serum pregnancy test at Screening and Day 1/Baseline and use two of the following acceptable methods of contraception until study termination:

a) Hormonal contraceptive: birth control pills, injection, patch, vaginal ring or implant;
b) Condom or diaphragm, with spermicide;
c) Intrauterine device (IUD)'
d) Sterile male partner (vasectomy performed at least 6 months prior to the study).

10.3.2. Men

If the Subject is a man who has not had a vasectomy, he and his female partner will be asked to practice appropriate contraception, as described above, during the study.

10.4. Clinical Laboratory Evaluations

Clinical laboratory (chemistry, hematology, urinalysis, serum pregnancy), pharmacokinetic and pharmacodynamic biomarker sample analysis will be performed by a central laboratory. **Table 2** summarizes the tests that will be performed.

The Investigator or medically qualified delegate will review the laboratory test findings and assess in writing whether any abnormal result (outside normal reference range) is clinically significant, i.e. associated with an adverse event and not the pre-existing medical history. In such cases, the associated adverse event must be detailed in source documentation and transcribed into the electronic Case Report Form (eCRF).

Table 2: 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
Differential (absolute, %)	Calcium	Protein
Leukocytes	Bicarbonate	Specific gravity
Basophils	Chloride	Turbidity
Eosinophils	Creatinine	Urobilinogen
Lymphocytes	Gamma glutamyl transpeptidase	Microscopic examination
Monocytes	Glucose	
Neutrophils	Lactate dehydrogenase	
Reticulocyte count*	Phosphorus	
	Potassium	
	Total protein	
	Sodium	
	Uric acid	
	Uric acid	
Other Laboratory Tests		
Serum pregnancy test (human chorionic gonadotropin)		
Pharmacokinetics: Plasma Cysteamine		
Pharmacodynamic Biomarkers: glutathione, glutathione disulfide, lactate		

10.5. Blood Volume

Assuming participation of the entire 24 months study, the estimated volume of blood drawn (in mL) per subject is provided below. If the Investigator suspects alcohol or drug abuse, or deems that additional lab tests are required for the follow-up of an adverse event, more blood samples may be collected.

Study Visit	Maximum # Visits	Chemistry & Hematology	PK	PD	Pregnancy	TOTAL without pregnancy tests	TOTAL with pregnancy tests
Day1 Visit	0 mL (blood was collected at previous Study RP103-MITO-001 Study Exit Visit)						
Quarterly Visit	7	4.5 mL	2 mL	4 mL	0.5 mL	73.5 mL	77 mL
Study Exit Visit	1	4.5 mL	2 mL	4 mL	0.5 mL	10.5 mL	11 mL
						84 mL	**88 mL**

10.6. 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 at the frequency specified in the Schedule of Events. 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.

The Investigator or medically qualified delegate will review the ECG tracings and assess in writing whether any abnormal result is clinically significant, i.e. associated with an adverse event and not the pre-existing medical history. In such cases, the associated adverse event must be detailed in source documentation and transcribed into the electronic Case Report Form (eCRF).

10.7. Physical Examinations

Physical examinations will be performed by the Investigator or medically qualified delegate at the frequency specified in the Schedule of Events. The physical examination will include assessments of general appearance, eyes, ears, nose and throat, chest (heart, lungs), abdomen (palpation, gastrointestinal sounds), extremities and skin. The exam will also include a basic neurological examination.

10.8. Vital Signs

Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, and oral body temperature) will be measured according to the Schedule of Events. 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.—Screening blood pressure may be retested 3 times at intervals of at least 5 minutes between each measurement. 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.

Head circumference measurement should be taken with a device that cannot be stretched, such as a flexible metal tape measure. Wrap the tape snugly around the widest possible circumference, from the most prominent part of the forehead (often 1-2 fingers above the eyebrow) around to the widest part of the back of the head. Try to find the widest way around the head. Re-measure 3 times, and take the largest number.

10.9. Adverse Event Inquiries

The active ingredient in RP103 (cysteamine bitartrate) has been associated with CNS symptoms such as seizures, lethargy, somnolence, depression and encephalopathy which are common in this patient population. At each study visit subjects will be queried about the occurrence of these specific symptoms since the previous visit using the Adverse Events Checklist provided in Section 15.5.

In addition, spontaneous adverse event reports will be identified initially by an open-ended, nondirective question.

10.10. Safety Review

Safety review of all adverse events will be performed periodically by the Investigator. Particular attention will be paid to potential CNS symptoms reported during the study. The investigator will assess such AEs for relationship to underlying disease versus relationship to study drug and determine appropriate action(s) to be taken.

10.11. Newcastle Paediatric Mitochondrial Disease Scale (NPMDS)

The NPMDS has been introduced to allow evaluation of the progression of mitochondrial disease in patients less than 18 years of age. (The Newcastle Mitochondrial Disease Scale (NMDS) provides a similar assessment tool for adult patients). In the paediatric population, demonstrating a genetic or biochemical basis for mitochondrial disease can be very difficult. Consequently we would recommend that the scale be administered to patients where there is a strong clinical suspicion of mitochondrial disease as well as those with a confirmed (biochemical or genetic) diagnosis. Repeated administration of the scale permits the longitudinal monitoring of these patients.

The aim of these disease rating scales is to standardize patient assessment and ensure accurate data collection. This information will provide an invaluable resource to help us understand the natural history of mitochondrial disease in children. It is predicted that the scale will also prove to be a useful tool for future clinical assessment of proposed treatments.

The rating scale encompasses all aspects of mitochondrial disease by exploring several domains: Current Function; System Specific Involvement; Current Clinical Assessment and Quality of Life. Almost every question in the scale has a possible score from 0-3: 0 representing normal, 1- mild, 2- moderate and 3- severe. In each case, examples of mild, moderate and severe impairment or disability are given.

There are three age-specific versions of the NPMDS, 0-24 months, 2-11 years and 12-18 years.

10.12. Investigational 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.

11. ASSESSMENT OF SAFETY

11.1. Definition and Grading Intensity of Adverse Events/Experiences

An adverse event/experience (AE) is defined as 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 AE that is reported after a dose of study drug.

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.

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

11.2. 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 United States FDA and competent authorities of any other participating countries.

Stopping Criteria (continued)

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, and possibly, probably or definitely related to study drug.

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:

- Two or more patients develop the same CTCAE Grade 3 adverse event;
- One patient develops a CTCAE Grade 4 adverse event;
- 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.

* Any death is an SAE by definition and must be reported to the Sponsor or Sponsor's representative designated to receive SAE reports. Whether or not the event or any other SAE is expected or unexpected will be assessed by Sponsor or its representative according to a pre-specified Safety Monitoring Plan (i.e., the current RP103 Investigator Brochure will be used as reference). It is the Sponsor or its representative's responsibility to make this assessment and to generate and distribute/submit any expedited regulatory reports as appropriate, e.g. IND Safety Reports and SUSARs.

11.3. 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 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 de-challenge 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 de-challenge or dose reduction (if performed) have occurred. Recurrence of symptoms on re-challenge (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 re-challenge (if performed).

11.4. Adverse Event Reporting

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 Institution identifier (i.e., Sponsor site number);
- Description of the event, action taken, and outcome;
- Date and time of onset 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 or opinion of causality; and
- Any other available diagnostic information that will contribute to the understanding of the event.

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.

The IRB or EC will be notified in writing (e.g., facsimile) by the Investigator per hospital procedures, within the required time frame as specified of an SAE requiring an expedited IND safety report, in accordance with 21 CFR 312.32.

11.5. Definitions

A serious adverse event (SAE) or reaction 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.

Medical judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical 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. These events should also usually be considered serious. 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.

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

The reporting period for adverse events is the period from signing the informed consent through 30 days after the last study drug administration. 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 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 final 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.

12. STATISTICAL PLAN

12.1. Statistical Methods

This open-label extension study is designed to assess the safety, tolerability and efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103) for treatment of children with inherited mitochondrial disease.

The sample size will be up to 25 subjects (the maximum number of participants planned for study RP103-MITO-001.

Any interim analyses will be described in detail in the statistical analysis plan (SAP), which will be developed and specify the statistical methods to be used. The SAP will be finalized prior to data cutoff or database lock for the subsequent analysis. Demographic and disposition data, drug administration, medical history, prior and concomitant medications, AEs, clinical laboratory measurements, vital signs, ECG measurements, physical examination findings, and all other safety data will be listed by subject and timepoint. Descriptive statistics will be tabulated for change and shift from Baseline in the safety laboratory variables (serum chemistry, hematology, and urinalysis), vital signs, [score names] scores and ECGs. Adverse events will be summarized by method of collection type, frequency, severity, relationship to study drug, any change in study drug administration, and number of subjects per treatment. 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.

12.2. Analysis Set

All subjects who receive at least one dose of study drug (RP103) will be included in the safety analysis set. All subjects who complete all protocol-specified study visits with evaluable efficacy data will be included in the efficacy analysis sets.

12.3. Sample Size Considerations

The sample size will be up to 25 subjects (the maximum number of participants planned for study RP103-MITO-001).

12.4. Accountability Procedure

Missing values will not be imputed.

12.5. Termination Criteria

All ongoing enrolled subjects will continue to be dosed until subject withdrawal, or the Investigator withdraws the subject from the study.

12.6. 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.

13. ADMINISTRATIVE ASPECTS

13.1. Change in Protocol

Unless absolutely necessary for safety of a patient, 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 and will not be implemented until regulatory and local (IRB/EC) approval are granted.

13.2. 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.

13.3. 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; ensure the proper completion and retention of source documentation, 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 (paper or email). 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 action items documented by the monitor in the site visit follow-up documentation (which may be in the form of a trip report or letter or email). Appropriate investigator responses include written documentation (paper or email) of corrective or preventive actions, eCRF or source documentation corrections, training records, or Memos to File; such documentation should be placed in the investigator study file or patient research file/chart, as appropriate.

13.4. 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 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.

13.5. 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.

13.6. 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. 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.

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, and the original will be maintained with the patient's records.

13.7. 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.

13.8. Quality Control and Quality Assurance

Accurate, consistent and reliable data will be ensured through the use of standard practices and procedures. Experienced clinical research associates (CRAs) will monitor the Investigators' source data against eCRF entries and verify that the data is accurate.

13.9. Archiving of Data

Patient files and other source data 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.

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15. Appendices

15.1. INSTRUCTIONS FOR CALCULATING BMI/BSA

- 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, or BSA in (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

15.2. PHARMACOKINETIC SAMPLE COLLECTION & PROCESSING

15.2.1. PK Sample Collection

For the analysis of plasma cysteamine, approximately 2 mL of blood will be collected in chilled (+2°C to +8°C) in a 2mL green-top evacuated collection tube containing sodium heparin.

Each PK sample tube label must include the protocol number, 5-digit subject ID number, collection date and nominal collection time.

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).

15.2.2. PK Sample Processing

Within 1 hour of collection, PK blood samples will be centrifuged at 2000g and 4°C for at least 10 minutes. The plasma will be split into two approximately equal volumes and placed into two different cryotube vials (one for PK analysis, and one back-up) and frozen at approximately –70°C or below.

Cryotube vials will be properly stored at approximately –70°C or below until shipment to the central laboratory. Each cryotube label must include the protocol number, 5-digit subject ID number, collection date, nominal collection time and the tube number (e.g. PK sample "1 of 2").

The two PK sample aliquots will be shipped to the laboratory in two different shipments (in case one is lost in transit), with sufficient dry ice to last the duration of transit.

15.3. PHARMACODYNAMIC SAMPLE COLLECTION & PROCESSING

15.3.1. PD Sample Collection

For analysis of the PD biomarkers, approximately 2 mL of whole blood will be collected for glutathione and glutathione-disulfide testing and 2 ml will be collected for lactate testing using the tubes provided.

Each sample tube label must include the protocol number, subject ID number, collection date and nominal collection time.

After collection, tubes will be mixed gently by inverting 7-8 and 8-10 times, respectively.

15.3.2. PD Sample Processing

PD blood samples will be prepared and stored as described in the central lab manual (or Study Reference Manual).

15.4. RP103 DOSING INSTRUCTIONS

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.

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:

- 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 (G-tube only; do not use GJ- or NG-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.***

RP103 DOSING IN LIQUID

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

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).

15.5. ADVERSE EVENTS CHECKLIST

The active ingredient in RP103 (cysteamine bitartrate) has been associated with CNS symptoms such as seizures, lethargy, somnolence, depression and encephalopathy which are common in this patient population. At each study visit (including the telephone visits at Week 2 and Week 6), subjects will be queried about the occurrence of these specific symptoms since the previous visit.

For each time point specified in the Schedule of Events (Protocol Section 2), the investigator or qualified designee will query the subject as to the presence or absence of the following symptoms. The interviewer should record the presence or absence of each adverse event in source documentation. Any positive response (present) must be assessed for relationship to underlying disease versus relationship to study drug.

- Skin rash
- Skin lesions
- Seizure
- Lethargy
- Somnolence
- Depression
- Encephalopathy
- Gastrointestinal ulceration and/or bleeding
- Nausea
- Vomiting
- Loss of appetite (anorexia)
- Diarrhea
- Fever
- Abdominal pain