27 June 2013
EMA/375807/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

PROCYSBI

International non-proprietary name: mercaptamine

Procedure No. EMEA/H/C/002465

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Marketing authorisation application

Name of the medicinal product:	PROCYSBI
Applicant:	Raptor Pharmaceuticals Europe BV Naritaweg 165 1043 BW Amsterdam THE NETHERLANDS
Active substance:	Mercaptamine bitartrate (synonym: cysteamine bitartrate)
International Nonproprietary Name:	mercaptamine
Pharmaco-therapeutic group (ATC Code):	Other alimentary tract and metabolism products (A16AA04)
Therapeutic indication(s):	PROCYSBI is indicated for the treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.
Pharmaceutical form(s):	Gastro-resistant capsule, hard
Strength(s):	25 mg and 75 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	60 capsules and 250 capsules

Table of contents

List of abbreviations

AE	Adverse Event
AR	Assessment report
AUC	Area under the plasma concentration curve
AUC_{0-t}	Area under the plasma concentration curve from zero to the last detectable sample
AUC_{0-inf}	Area under the plasma concentration curve from zero to infinity
CB	Cysteamine bitartrate
C_{max}	Maximum plasma concentration
CYP	Cytochrome P450 enzyme
EMA	European medicines agency
F_{rel}	Relative bioavailability
ITT	Intention to treat
LC-MS/MS	Liquid chromatography assay with tandem mass spectrometric detection
LLOQ	Lower limit of quantitation
MAO	Monoamine oxidase
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-protocol
PPIs	Proton pump inhibitors
Q6h	One dose every 6 hours
Q12h	One dose every 12 hours
RP103	PROCYSBI, gastroresistant delayed release cysteamine bitartrate
SmPC	Summary of product characteristics
SOC	System organ class
TEAEs	Treatment emergent adverse events
t_{max}	Time to maximum plasma concentration
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Raptor Pharmaceuticals Europe B.V. submitted on 1 March 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for PROCYSBI, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 November 2010.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

“the management of proven nephropathic cystinosis in children and adults. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of cystinosis patients and, when treatment is started early, it delays the development of renal failure”

PROCYSBI, was designated as an orphan medicinal product EU/3/10/778 on 20 September 2010. PROCYSBI was designated as an orphan medicinal product in the following indication: treatment of cystinosis.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of PROCYSBI as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a therapeutic equivalence study (non-inferiority design) with the reference medicinal product Cystagon and appropriate non-clinical and clinical data.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Cystagon, 150mg, 50mg, hard capsules
- Marketing authorisation holder: Orphan Europe SARL
- Date of authorisation: 23-06-1997
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/97/039/001

Protocol assistance

The applicant received Protocol assistance from the CHMP and COMP on 09 November 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

PROCYSBI was not licensed in any country at the time of submission of the application. A New Drug Application was filed in the USA on 30 March 2012.

Accelerated procedure

The Applicant requested an accelerated review which was not granted by the CHMP.

1.2. Manufacturers

Manufacturer responsible for batch release

Almac Pharma Services Ltd.
20 Seagoe Industrial Estate
Craigavon
County Armagh
BT63 5UA
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Tomas Salmonson Co-Rapporteur: David Lyons

- The application was received by the EMA on 1 March 2012.
- The procedure started on 21 March 2012.

- The Rapporteur's initial Assessment Report was circulated to all CHMP members on 8 June 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012.

- During the meeting on 19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July 2012.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 January 2013.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 March 2013.

- During the CHMP meeting on 21 March 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 29 April 2013.

- The rapporteur circulated the assessment report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 24 May 2013.

- During the CHMP meeting on 30 May 2013, the CHMP agreed on a 2nd List of Outstanding Issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP consolidated 2nd List of Outstanding Issues on 05 June 2013.

- During the meeting on 27 June 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to PROCYSBI.

2. Scientific discussion

2.1. Introduction

Cystinosis is an autosomal recessive congenital error of metabolism in which cystine transport from the lysosomes is reduced or absent. Cystine is accumulated intracellular and crystals are formed that damages various organs, in particular, the kidneys leading to progressive glomerular failure (renal Fanconi syndrome). Patients with cystinosis also generally suffer from growth failure, rickets and photophobia (due to cystine deposit in the cornea). Cystine is also accumulated in a number of cells apart from the kidney e.g. brain, cornea, conjunctiva, bone marrow, lymphatic nodes, leucocytes, and other organs.

The diagnosis of cystinosis is made by measuring the leukocyte cystine level, a biomarker and the surrogate marker used to manage patients with cystinosis. Oral cysteamine therapy provides the mainstay of cystinosis treatment aiming for a leukocyte cystine level < 1.0 nmol ½ cystine/mg protein.

Healthy subjects have white blood cells (WBC) levels of 0.2 nmol ½ cystine/mg protein while untreated patients with cystinosis have elevated levels > 2 nmol ½ cystine/mg protein.

Lysosomal cystine accumulation in cystinosis results from the defective transport of cystine across the lysosomal membrane.

Mercaptamine is an aminothiol reacting with lysosomes resulting in a thiol-disulfide interchange reaction in where intracellular cystine is converted to cysteine and cysteine-cysteamine mixed disulfide. Both these latter substances can exit the lysosome in patients with cystinosis.

Currently Cystagon, containing mercaptamine (also known as cysteamine), in the form of bitartrate salt, is the only approved treatment for cystinosis. Cystagon has been approved in the US since 1994 and in the EU since 1997. Cystagon is approved for the treatment of nephropathic cystinosis in children and adults. The maintenance dose of Cystagon should be divided in four doses and be given every 6 hours.

PROCYSBI is presented as gelatine capsule filled with enteric coated beads containing the same active substance as Cystagon, mercaptamine bitartrate.

PROCYSBI has been developed as a delayed-release formulation (RP103) that should be dosed twice daily. This would lead to increased compliance and better quality of life for patients with cystinosis. Furthermore, for patients that have difficulties swallowing capsules, the beaded encapsulated formulation allows the content of the capsules to be sprinkled or mixed with food and mixed with liquids.

The assessment of the efficacy and safety of PROCYSBI delayed-release formulation was based on a clinical program, comprising of 5 clinical studies, including 2 bioequivalence studies comparing the bioavailability of PROCYSBI when administered as capsule and sprinkled on food, 1 phase IIb study intended to investigate the PK and tolerability of the new formulation, 1 phase III efficacy/safety study intended to show non-inferiority when compared with Cystagon and one safety extension study.

2.2. Quality aspects

2.2.1. Introduction

PROCYSBI is presented as gastro-resistant hard capsules containing 25 or 75 mg of mercaptamine (also known as cysteamine), in the form of bitartrate salt, as the active substance. Mercaptamine is contained in microspheronised core beads that are enteric coated and encapsulated in size 3 or size 0 hard gelatine capsules for the 25 mg and 75 mg strengths, respectively. The 25 mg capsules are light blue imprinted “25 mg” in white ink and a light blue cap imprinted with Raptor Logo in white ink. The 75 mg capsules are light blue imprinted “75 mg” in white ink and a dark blue cap imprinted with Raptor Logo in white ink.

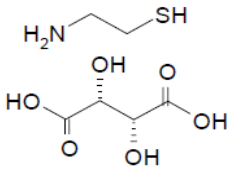
Excipients used for preparation of PROCYSBI gastro-resistant hard capsules are well known and commonly used for preparation of modified release oral dosage forms. Excipients used for the enteric coated core beads (capsule content) include microcrystalline cellulose, Eudragit L 30 D-55 (methacrylic acid and ethyl acrylate copolymer, sodium lauryl sulfate, and polysorbate 80), hypromellose, talc, triethyl citrate and sodium lauryl sulphate. Hard capsules are composed of gelatine, titanium dioxide and indigo carmine. Capsules are imprinted with

white ink consisting of shellac, povidone, titanium dioxide and solvents which are removed during imprinting.

The capsules are packed in high density polyethylene (HDPE) bottles fitted with one 2-in-1 desiccant cylinder and one oxygen absorber cylinder, with a child resistant polypropylene (PP) closure.

2.2.2. Active substance

Mercaptamine (INN), also known as cysteamine (USAN name) is chemically designated as ethanethiol or 2-amino[R-(R*, R*)]-2,3-dihydroxy-butanedioate, and has the following structure:



Mercaptamine bitartrate is a white crystalline powder, freely soluble in water. The substance does not exhibit isomerism as there is no chiral centre and no polymorphic forms have observed.

Particle size was not considered a critical quality attribute of the active substance as mercaptamine bitartrate is freely soluble in water and is dissolved to form a wet blend with the excipients (to generate an extrudate) during the manufacturing process of the finished product.

Confirmation of the chemical structure of cysteamine bitartrate was provided by elemental analysis (confirmation of the determined elementary composition by evaluation of C, H, N, S and O content), IR, 1H-NMR, 13C-NMR as well as by mass spectral analysis. The IR, NMR and MS spectrum assignations were consistent with the declared chemical structure

In addition the potential for polymorphism has been investigated. The substance was characterised by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and thermogravimetry (TGA).

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

Information about manufacturing process of mercaptamine bitartrate has been provided using Active Substance Master File (ASMF) procedure. The synthesis is short and do not contain any step involving formation of covalent bonds. The manufacturing process and process controls were, however, considered acceptable due to the long experience by the manufacturer and the nature and low complexity of the active substance. Detailed information on the manufacturing process, materials, critical steps and intermediates, process validation and manufacturing process development have been provided in the restricted part of the ASMF and it was considered satisfactory.

In general, sufficient information regarding the manufacturing process, starting materials, critical steps and manufacturing process development have been provided. The synthesis and process parameters have been well characterised and described.

Specification

The active substance specification includes tests for physical appearance, solubility, colour of solution (UV), identification (HPLC and melting point), residue on ignition, chlorides content, water content (Karl Fisher), assay – mercaptamine free base and tartrate counter ion (HPLC), related substances (HPLC), residual solvents (GC) and particle size distribution (laser diffraction).

A detailed description for all analytical methods was provided. Some of the proposed methods are in accordance with the Ph. Eur. Complete method validation data was provided for the non compendial (*in-house*) analytical methods. In general specification limits and analytical methods proposed are suitable to control the quality of the active substance.

Potential impurities have been well discussed in relation to their origin (raw material, manufacturing process and degradation products) and potential carry-over into the final active substance. Impurities have been demonstrated to be sufficiently controlled by the applied analytical methods, the specifications, and the manufacturing process.

Batch analysis results for 9 commercial scale batches of mercaptamine bitartrate have been presented. All batches were manufactured by the proposed commercial manufacturer according to the process described in the ASMF. Data demonstrated consistency between batches and that all batches comply with the proposed specification. It can be concluded that the batch analysis results indicate that the manufacturing process is reproducible and under control.

Stability

Three commercial scale batches of cysteamine bitartrate manufactured by the proposed manufacturer have been placed on accelerated (40°C/75% RH) and long-term (25°C/60%RH) stability testing according to the ICH requirements. The active substance batches in the stability studies were packaged in the proposed packaging system. Results after storage for three months under long term and accelerated conditions were presented.

In addition, forced degradation studies were conducted on the active substance, which demonstrated that the analytical methods are stability indicating (mass balance and peak purity are achieved) and which determined that the active substance is prone to degradation under thermal, basic and oxidative conditions.

Only three months stability data were provided for the active substance and this information was insufficient to propose any retest period for cysteamine bitartrate. Therefore no retest period for the active substance was established, mercaptamine bitartrate must be tested prior to use.

2.2.3. Finished medicinal product

Pharmaceutical development

The objective was to develop an enteric coated dosage form with the flexibility to administer the product to young children by sprinkling into foodstuffs or via a gastric feeding tube. The starting point of the formulation development was the known composition of the authorised immediate release product Cystagon (the reference product). The expected benefit from an enteric coated product compared to the available immediate release product was a reduction in the frequency of administration for patients (from every 6 hours to every 12 hours). The most suitable target dosage form was determined to be enteric coated beads encapsulated in gelatine capsules.

The active substance is highly water soluble and makes up significant amount of the formulation of the enteric coated beads. The manufacturing process required manufacture of a wet mass suitable for extrusion and spheronization and standard formulation excipients were chosen. Microcrystalline cellulose was chosen as a filler as it provided sufficient strength to withstand collision during spheronization and has plasticizing characteristics to form spherical beads from cylindrical exudates – formulations with different concentrations were investigated until the optimum amount was determined. With regards to the enteric coating, Eudragit L 30 D-55 was selected as this coating agent was used in the early development studies. The level required was optimised in relation to the desired dissolution characteristics.

The formulation of the product has not changed since manufacture of the first batch. The clinical studies were performed using batches with product of the proposed composition manufactured via the proposed manufacturing process.

The finished product is required to have the flexibility of administration to either swallow the capsules whole, or to open the capsule and sprinkle the contents onto food or to deliver these via a gastric feeding tube. The bead size was determined in relation to the FDA's Draft Guidance for Industry: Size of Beads in Drug Products Labelled for Sprinkle (2012). The bead particle size is routinely controlled as an in-process control test during manufacturing of the product.

Administration of the capsule contents (beads) through a gastric feeding tube was also evaluated. The study demonstrated that coated beads are suitable for administration through a feeding tube. Liquids and/or food used must be selected from the one shown comparability with the finished product. The beads should be delivered at a slow rate.

In addition a study was conducted to demonstrate compatibility of the capsule contents (sprinkled) with a number of food and liquids commonly used by patients. Food and liquids with pH ≤ 5.5 were selected as the Eudragit coating dissolves at a pH above 5.5. As a result, a maximum holding time of two hours was recommended for food (applesauce, peanut butter and yoghurt). The beads/yoghurt mixture may be stored at room temperature or 5°C. Frozen foods are not acceptable.

The compatibility of the enteric coated beads with tap water (the most commonly used vehicle for administration) was also performed. It was established that addition of 25 drops (1/4

teaspoon) of lemon concentrate were required to reduce the pH of tap water to 3.5 to prevent changes in the coating (softening, swelling or agglomeration of the coating).

Manufacturing process development has been comprehensively documented and found acceptable, no significant problems were encountered during scale up from pilot to commercial scale batches, and process parameters have been appropriately optimised. The choice of the process was considered justified and the critical process parameters and process equipment were generally satisfactorily identified. It has been shown that the manufacturing process was robust.

It can be concluded that the formulation development of the product was satisfactorily described. The key critical parameters were identified and successfully evaluated.

Adventitious agents

Among excipients used in the medicinal product gelatine (component of the capsule shell) is of animal origin. Ph. Eur. TSE Certificates of Suitability were provided for gelatine.

Lauryl sulphate and polysorbate 80 are of vegetal origin and relevant certificates from manufacturers of this excipient have been provided.

Manufacture of the product

The manufacturing process is standard and consist of 8 steps .

Overall, description of the manufacturing process was adequate. Critical steps have been identified and properly evaluated at the commercial scale. The reproducibility of the process has been suitably demonstrated.

A process validation protocol was provided, and it includes the steps from bead preparation through to encapsulation. In addition, supportive evaluation/validation studies were performed during scale up to evaluate and develop the equipment parameters for the process. All manufacturing unit operations were evaluated. Four commercial scale batches were manufactured in accordance with this protocol and three of these were placed on stability studies.

Formal validation, in accordance with the agreed protocol, will be performed post-approval on 3 consecutive production scale batches. Since the manufacturing process is standard and it has been extensively evaluated and the critical process parameters for the process have been identified it was considered sufficient to provide a validation protocol and perform the validation post-approval.

Product specification

The finished product is controlled by testing attributes relevant for this dosage form. The finished product specification includes tests for appearance, identity of the active (Near-IR and HPLC), uniformity of dosage units, assay (HPLC), related substances (HPLC), acid resistance (HPLC), dissolution (HPLC), water content (Karl Fisher) and microbial purity.

The proposed specifications were justified based on the batch and stability results and are generally adequate for assuring the product quality and therefore were accepted.

The specification proposed for the finished product is complete and fulfil the requirements of the Ph. Eur. monograph for capsules and ICH Q6A. Limits for assay and related substances were established in accordance with ICH Q3B requirements. A detailed description for all analytical methods was provided. Full method validation in accordance with the ICH Q2 requirements was performed for the non compendial (*in-house*) analytical methods.

Batch analysis data have been provided for 22 batches of 25 mg and 75 mg product, which were manufactured from 13 batches of gastro-resistant beads of which 11 were of full commercial scale. Batch analysis results demonstrated compliance with the proposed specifications and confirmed consistency and uniformity of the product. The results were consistent from batch to batch and proved that the product can be manufactured reproducibly according to the agreed specifications.

Stability of the product

Stability studies have been initiated according to ICH guidelines on 3 production scale batches of each strength packaged in its commercial packaging. Data were provided from six months of accelerated conditions (40°C/75% RH) and 18 months of long term conditions (25°C/60 % RH). No significant changes or trends in any of the parameters monitored have been seen and all data are within proposed specifications.

A coated bead hold study was conducted to support the storage of coated beads. No significant trend was observed in the coated beads over the course of the study.

Furthermore an in-use stability study, designed to mimic the use of the product by patients, was conducted to demonstrate that the container closure system was suitable during patient use. No significant change in assay was observed. The container closure system was found suitable for the use of the product by patients through the expected life of each bottle.

The overall stability data showed that PROCYSBI gastro-resistant hard capsules were stable under all tested conditions. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The information provided about the active substance, mercaptamine (also known as cysteamine), was of acceptable quality. In general sufficient information regarding the manufacturing process, materials, critical steps and intermediates, process validation and manufacturing process development have been provided. The synthesis and process parameters have been well characterised and described.

Specification limits and analytical methods are suitable to control the quality of the active substance.

No re-test period for the active substance was established as stability data were not sufficient. Mercaptamine bitartrate must be tested prior to use.

The pharmaceutical development of the finished product has been satisfactorily described. Formulation development was well described, and focussed on producing a dosage form which was enteric coated, but which had the flexibility to administer the product to young children by

sprinkling into foodstuffs or administration via gastric tubes. The compatibility of the product with both of these routes of administration and with different foodstuffs and liquids has been adequately investigated. Physicochemical and biological properties of the finished product have been well analysed, and the critical parameters for performance of the product have been defined and are routinely controlled, namely acid resistance, solubility in neutral pH solutions and bead particle size.

The method of manufacture is considered standard and has been satisfactorily described, including in-process tests. The data shows consistent manufacture and is considered sufficient for this manufacturing process. A satisfactory validation protocol has been provided.

The proposed specifications were justified based on the batch and stability results, and are in general adequate for assuring the product quality and therefore were accepted.

The stability program is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance (mercaptamine) and the finished product (gastro-resistant hard capsules containing 25 or 75 mg of mercaptamine) have been appropriately characterised and generally satisfactory documentation has been provided. The results indicate that mercaptamine as well as the capsules (and their contents) can be reproducibly manufactured. Therefore the product should have a satisfactory and uniform performance.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. However, a bacterial reverse mutation assay study (RP103-NCL-01A) was done with the drug substance used for RP103. In addition, a DEREK analyses was performed in order to determine whether any of newly identified (but previously present in Cystagon) impurities in gastro-resistant hard capsules of mercaptamine (as mercaptamine bitartrate), presented any structural alerts. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

The mechanism of action has been characterised in vitro and is supported by long term clinical use, which taken together support the indication for treatment of cystinosis. No new safety pharmacology studies have been performed by the applicant. The overview consists of a

literature review. Central nervous system (CNS) effects were noted in mice following intraperitoneal injection from 12.5 to 200mg mg/kg, whereas 1200 mg/kg caused seizures and death. Depletion of brain noradrenaline and somatostatin occurred following 30 mg/kg sc injection of cysteamine, and at higher doses depleted prolactin from the pituitary. Substantial gastrointestinal ulceration was observed at supratherapeutic doses in mice, and in rats with ED50s of 325 (sc) and 650 (oral) mg/kg for gastric and duodenal ulcers respectively. Effects on cardiovascular effects may be dependent on dose, as blood pressure was only increased with high doses of cysteamine, but a chronic dose of 48.3 mg/kg for 6 months in rats.

2.3.3. Pharmacokinetics

The applicant did not conduct any pre-clinical studies on absorption and pharmacokinetics of cysteamine. The absorption of cysteamine was not described by the applicant.

The distribution metabolism and excretion data is limited, but suggest cysteamine distributes primarily to the kidney, liver, small intestine and pancreas in mice. Six urinary metabolites were identified in mice, but there is no comparable clinical data submitted to determine if these are the major human metabolites. Studies suggest cysteamine disappears rapidly from the blood and that drug excretion is primarily in the urine.

2.3.4. Toxicology

Single dose toxicity

The single-dose toxicology studies showed acute systemic toxicity following 660 mg/kg oral administration to rats. As no non-lethal dose was described, no LD_{50} can be determined for oral dosing in rats. This dose was supratherapeutic and as the safety of cysteamine bitartrate has been established clinically, the acute systemic toxicity of this formulation is not considered a concern.

Repeat dose toxicity

The 4-week repeat-dose study in monkeys was limited by the very small treatment group size (n=1) and the lack of an adequate control group, as both animals received cysteamine and one animal was pre-treated with an unknown compound. One animal showed a variety of adverse effects including CNS effects, bloody stools and tachycardia following treatment on day 11. In the 59-week study in monkeys gastrointestinal and liver toxicities were the primary observations. Gastrointestinal effects were limited to transient emesis and soft stools at the lowest dose of 20 mg/kg/day which is subtherapeutic, but as gastrointestinal effects are well described clinically the lack of safety margin is acceptable.

Genotoxicity

Cysteamine was not mutagenic in the Ames test. It produced a negative response in an *in vitro* sister chromatid exchange assay in human lymphocytes, but a positive response in a similar assay in hamster ovarian cells. The positive result in CHO cells is balanced by the negative result in human lymphocytes at similar concentrations of cysteamine.

The applicant has performed the following studies:

- DEREK analyses

In order to determine whether any of newly identified (but previously present in Cystagon) impurities in gastro-resistant hard capsules of mercaptamine (as mercaptamine bitartrate) presented any structural alerts, an in silico analysis was performed of six compounds.

Endpoints searched were: Genotoxicity, mutagenicity, chromosome damage, carcinogenicity.For all six of these known impurities, the report conclusion was: For the qualification of impurities the main concern is the presence of a DNA-reactive genotoxic carcinogen. No Derek alerts for genotoxicity, mutagenicity, chromosome damage or carcinogenicity were present in Raptor Impurity [1, 2, 3, 4, 5 or 6, depending on the specific compound of the report]. Based on these findings this impurity can be classified as a category 5 impurity with no alerting features (1, 2, 3) and can be qualified as an ordinary (non-genotoxic) impurity.

- Bacterial Reverse Mutation Test

The test article, mercaptamine bitartrate, was tested in the Bacterial Reverse Mutation Assay using Salmonella typhimurium tester strains TA98, TA100, TA1535 and TA1537 and Escherichia coli tester strain WP2 uvrA in the presence and absence of Aroclor induced rat liver S9. The assay was performed in two phases, using the plate incorporation method. The first phase, the preliminary toxicity assay, was used to establish the dose range for the mutagenicity assay. The second phase, the mutagenicity assay, was used to evaluate the mutagenic potential of the test article. Dosing formulations were adjusted for free base, using a correction factor of 3.93.

Based on the findings of the toxicity assay, the maximum dose tested in the mutagenicity assay was 5000 µg per plate.

In the mutagenicity assay, no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation. The dose levels tested were 50, 150, 500, 1500 and 5000 µg per plate. Neither precipitate nor toxicity was observed.

Under the conditions of this study, test article mercaptamine bitartrate was concluded to be negative in the Bacterial Reverse Mutation Assay.

Carcinogenicity

Carcinogenicity studies were not undertaken by the applicant. Cysteamine has not been tested for its carcinogenic potential in long-term animal studies.

Reproduction toxicity

Cysteamine at 750 mg/kg/day in female and/or male adults decreased conception rates, and live births were lower in groups where either both sexes or only females, were treated. Survival was also decreased in animals weaned by treated adults, suggesting toxicity during the lactation period. In two separate studies where animals were orally administered 75 or 375 mg/kg/day cysteamine, the high dose was found to reduce conception, the number of live pups per litter, pup body weight and survival.

In teratogenicity studies presented in the dossier of the reference product, 37.5 to 150 mg/kg/day, cysteamine bitartrate has been reported to be teratogenic and fetotoxic in rats. In another fertility and early embryonic developmental study, there were no adverse effects on reproductive performance with respect to conception and early embryonic development at up to 150 mg/kg/day cysteamine, although some maternal toxicity was seen. In an embryo-fetal development study, cysteamine was teratogenic at 100 and 150 mg/kg/day. Specific malformations included cleft palate and kyphosis, as well as intrauterine growth retardation.

2.3.5. Ecotoxicity / environmental risk assessment

Cysteamine bitartrate is freely soluble in water and the logKow can thus be assumed to be low. Screening for persistence, bioaccumulation and toxicity is therefore not considered to be necessary. Furthermore, cysteamine is a degradation product of the amino acid cysteine and may therefore be considered to be a natural compound similarly to amino acids, peptides, proteins and therefore the CHMP considered that an ERA is not needed.

However the applicant has performed a phase I Environment Risk Assessment.

The elimination of unchanged cysteamine in the urine has been shown to range between 0.3 % and 1.7% of the total daily dose in patients; the bulk of cysteamine is excreted as sulphate.

Therefore, for the purpose of this ERA, the applicant made the assumption that 100% of RP103 is excreted in urine in free or sulfated form. Thus, the main route of release to the environment is waste water.

Since the calculated PEC SURFACEWATER = 1.5 10-8 mg/L was well below 0.01µg/L, the applicant considered that a Phase II environmental effect analysis is not required. The CHMP agreed with this conclusion.

Moreover, no increase in the use of cysteamine is expected since the product is intended to substitute for other marketed product containing the same active substance and it does not contain any components that would result in additional hazard to the environment. Gastro-resistant hard capsules of mercaptamine (as mercaptamine bitartrate)is therefore not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The absorption of cysteamine was not described by the applicant. Clinical studies to compare the PK of PROCYSBI to the reference product demonstrated that absorption is consistent with a delayed-release formulation, with a slower rate of absorption and elimination than the reference product. As the absorption of this cysteamine bitartrate formulation is known, the absence of non-clinical absorption data is acceptable.

High doses of cysteamine, either by oral or parenteral routes, produce duodenal ulcers in rats and mice but not in monkeys. Experimental administration of the drug causes depletion of somatostatin in several animal species. The consequence of this for the clinical use of the drug is unknown.

In teratogenicity studies presented in the dossier of the reference product, 37.5 to 150 mg/kg/day, cysteamine bitartrate has been reported to be teratogenic and fetotoxic in rats. In an embryo-foetal development study, cysteamine was teratogenic at 100 and 150 mg/kg/day. Specific malformations included cleft palate and kyphosis, as well as intrauterine growth retardation. In two separate studies where animals were orally administered 75 or 375 mg/kg/day cysteamine, the high dose was found to reduce conception, the number of live pups per litter, pup body weight and survival. The reproduction toxicity findings are adequately reflected in the relevant sections of the SmPC.(sections 5.3 and 4.6)

Genotoxicity studies have been published using cysteamine, induction of chromosome aberrations in cultured eukaryotic cell lines has been reported, specific studies with cysteamine did not show any mutagenic effects in the Ames test or any clastogenic effect in the mouse micronucleus test. A bacterial reverse mutation assay study ("Ames test") was performed by the applicant with the cysteamine bitartrate used for PROCYSBI and cysteamine bitartrate did not show any mutagenic effects in this test.

A reduction of fertility was observed in rats at 375 mg/kg/day, a dose at which body weight gain was retarded. At this dose, weight gain and survival of the offspring during lactation was also reduced.

Carcinogenicity data has not been submitted, and the lack of data is described in section 5.3 of the SmPC. Considering clinical use of the reference product since its authorisation in 1997 has not revealed any carcinogenic potential, and that the cystinosis is a fatal disease, the lack of studies is found acceptable by the CHMP.

The only difference between PROCYSBI and the already marketed medicinal product Cystagon is the delayed-release formulation of cysteamine bitartrate gastro-resistant hard capsule, consisting of capsules containing enteric-coated granules. The difference in formulation does not suggest the need of generating any new non-clinical data in addition to the available literature and Cystagon non-clinical data.

2.3.7. Conclusion on the non-clinical aspects

A summary of the literature overview on non-clinical data for mercaptamine bitartrate was provided. In addition cross-reference to the non-clinical safety and efficacy of the reference product was made and was accepted by the CHMP. In addition the applicant conducted a bacterial reverse mutation assay study. Mercaptamine bitartrate gastro-resistant hard capsules is not expected to pose a risk to the environment. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for gastro-resistant hard capsule containing mercaptamine bitartrate (RP103).

The goal of the clinical development plan for PROCYSBI is to demonstrate comparable efficacy in controlling white blood cell (WBC) cystine level between RP103 (gastro-resistant hard capsule) and Cystagon, the reference product.

Formal protocol assistance by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

To support the marketing authorisation application the applicant conducted the following studies (see Table 1):

1) A single dose, phase 2b study (RP103-01) in patients with cystinosis, to investigate the PK (i.e., C_{max}, T_{max} and AUC), PD (i.e., WBC cystine levels), and potential safety and tolerability of RP103 compared with Cystagon;

2) A cross-over, randomized pivotal phase III study (RP103-03) to demonstrate safe, non-inferiority efficacy of gastro-resistant capsules administered every 12 hours vs. Cystagon in patients with cystinosis;

3) A safety/efficacy extension study (RP103-04) that allowed patients enrolled in study RP103-03 to continue using PROCYSBI until it is commercially available;

4) Four bioequivalence (BE) studies (RP103-02, RP103-05, RP103-06 and RP103-09), the first one (RP103-02) in fed healthy volunteers. The second and third BE studies (RP103-05 and RP103-06), in fasted healthy volunteers, to demonstrate that RP103 capsules taken as a whole capsule are bioequivalent to RP103 capsules sprinkled on food (applesauce and/or orange juice). The forth BE study (RP103-09)to compare the rate and extent of absorption of the delayed-release capsules (RP103) following a single dose of 600 mg administered under two different fasted conditions: taken alone and taken with the fifth consecutive daily dose of the proton pump inhibitor omeprazole.

Three bioequivalence studies (RP103-02, RP103-05 and RP103-06) were necessary to demonstrate bioequivalence between dosing RP103 as a whole capsule to its content sprinkled on applesauce and/or orange juice. The results of the first study (RP103-02) in fed healthy volunteers were non-interpretable due to the discovery of a food effect. Therefore a second and a third BE studies (RP103-05), in fasted healthy volunteers, were conducted in order to demonstrate that RP103 capsules taken as a whole capsules are bioequivalent to RP103 capsules sprinkled on a small amount of food (applesauce and/or orange juice).

At the CHMP request and in order to address the concern that the gastro-resistant capsules which are designed to dissolve at pH ≥5.5 might not by-pass the stomach in patients taking proton pump inhibitors (PPIs), a formal interaction study between RP103 and a PPI was

needed in order to support the posology instructions. The forth BE study (RP103-09) was carried out in order to compare the rate and extent of absorption of the delayed-release capsules (RP103) following a single dose of 600 mg administered under two different fasted conditions: taken alone and taken with the fifth consecutive daily dose of the proton pump inhibitor omeprazole.

Table 1. Tabular overview of clinical studies

Type of Study	Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
PK; initial tolerability	RP103-01	Safety and tolerability; inform the design of pivotal study RP103-03	Single center, single dose, open label, non-randomized	RP103 single dose of 75mg capsule vs. Cystagon single dose of 150mg capsule; oral	9	Patients with nephropathic cystinosis	Single dose	Completed
Bioequivalence	RP103-02	Demonstrate bioequivalence of intact capsules vs. capsule contents	Single center, randomized, crossover, fed	RP103 single dose of each route of administration; Intact capsules vs. capsule contents mixed with food	18	Healthy Volunteers	3 weeks	Completed
Efficacy & Safety (pivotal)	RP103-03	Demonstrate non-inferiority of RP103 vs. Cystagon in reducing WBC cystine	Multi-center, randomized, crossover	RP103 Q12H vs. Cystagon Q6H; Oral	43 randomized	Patients with nephropathic cystinosis	9 weeks	Completed
Safety (extension)	RP103-04	Long-term safety and tolerability	Multi-center, long-term, open label	RP103 Q12H; Oral	60	Patients with nephropathic cystinosis	Up to 36 months	Ongoing
Bioequivalence	RP103-05	Demonstrate bioequivalence of intact capsules vs. capsule contents; PK profile of two different meal delays	Single center, randomized, crossover, fasted	RP103 single dose of each route of administration; Intact capsules vs. capsule contents, both administered with food	20	Healthy Volunteers	2 weeks	Completed
Bioequivalence	RP103-06	Demonstrate bioequivalence of intact capsules vs. capsule contents	Single-center, randomized, crossover, fasted	RP103 single dose of each route of administration Intact capsules (administered with orange juice) vs. capsule contents mixed with food (applesauce plus orange juice)	20	Healthy Volunteers	2 weeks	Completed
Bioequivalence	RP103-HLTA-009	Demonstrate bioequivalence of RP103 administered alone, then with a proton pump inhibitor	Single center, sequential, fasted	RP103 single dose alone (Day1); then RP103 single dose with Omeprazole (Day6); Intact capsules administered with orange juice.	20	Healthy Volunteers	1 week	Completed

2.4.2. Pharmacokinetics

- **Protocol Number**: RP103-02

Study Title: A Randomized, Open-Label, 2-way Crossover, Single-Dose, Sequential Design Study to Evaluate the Bioequivalence of Two Different Modes of Administration of Cysteamine Bitartrate Delayed-release Capsules (RP103) Following a 600 mg Dose in Healthy Subjects Under Fed Conditions

Methods

Study design

Investigator and Study Center: Shanthini Daniel, MD, Jasper Clinic, Inc. Kalamazoo, MI

Objectives: 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 [Treatment B] and 2) content of opened delayed-release capsules [Treatment A].

Methodology: This was a single center, bioequivalence, open-label, randomized, 2-period, 2-sequence, crossover study. 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 of Treatment A/Treatment B for area under the concentration-time curve from time 0 to infinity ($AUC_{(0\text{-}inf)}$), area under the concentration-time curve from zero to t, the time of the last measurable concentration ($AUC_{(0\text{-}t)}$), or maximum observed plasma concentration (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; 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. The study was stopped following Stage 3.

Stage 3 was conducted at the same clinical site as Stage 1, and the same protocol requirements and procedures were followed with the exception that subjects were dosed under fasted conditions.

Treatment A: The contents of opened 8 x 75 mg cysteamine bitartrate delayed-release capsules administered mixed with pudding

Treatment B: 8 x 75 mg cysteamine bitartrate delayed-release capsules swallowed intact

Duration of Treatment: For Stage 1, Treatments A and B were administered in a randomized crossover fashion in 2 study periods. Each subject received a single 600 mg dose of study drug (RP103) on Day 1 of Period 1, followed by a 6-day washout, and then a second single 600 mg dose of study drug (RP103) was given on Day 1 of Period 2. For Stage 3, four subjects who had completed Stage 1 returned to receive intact capsules in a fasted state.

The planned/actual single oral cysteamine dose was 600 mg in each period, administered in the fed state. Treatments were randomized so that subjects received either Treatment A or Treatment B administered after a high fat breakfast on Day 1 of each study period of Stage 1. Four subjects were re-admitted for Stage 3 and received Treatment B (intact capsules) administered in the fasted state.

Test and reference products

Drug Product: RP103, Cysteamine bitartrate (equivalent to 75 mg cysteamine free base) delayed-release capsules containing microspheronized beads manufactured by Patheon Pharmaceuticals, Inc., Cincinnati, Ohio for Raptor Pharmaceuticals Inc.

Population studied

Up to 38 healthy volunteers, male or female, smokers or nonsmokers were planned for inclusion into the study. Seventeen of 18 subjects completed both Periods 1 and 2 of Stage 1 (1 subject withdrew following Period 1). Stage 2 was to include 20 subjects; however Stage 2 was not conducted. Stage 3 included 4 subjects previously enrolled in Stage 1.

Analytical methods

Plasma samples containing sodium heparin as the anticoagulant were analyzed for cysteamine using protein precipitation extraction with acetonitrile and liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The analytical method was developed and validated and has a calibration range of 75.0 to 10,000 ng/mL.

Pharmacokinetic variables

Blood samples for measurement of cysteamine in plasma were drawn relative to each single dose as follows: 0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18 and 24 hours after study drug administration.

Samples were collected into chilled collection tubes containing sodium heparin, and were stored on wet ice until centrifuged within 30 minutes of collection. Tubes were centrifuged at 2000g and 4ºC for 10 minutes. The resultant plasma was split equally into 2 aliquots and transferred into chilled 1.0 mL polypropylene CryoTubes. All CryoTubes were transferred to the freezer within 1 hour of collection and stored at approximately -70º C until shipment. Frozen aliquots were shipped under dry ice for analysis.

The following PK parameters were estimated from the plasma concentration-time profiles based upon actual collections times:

$AUC_{(0-t)}$ - area under the concentration-time curve from time 0 to t, the time of the last measurable concentration

$AUC_{(0-inf)}$ - area under the concentration-time curve from time 0 to infinity

F_{ext} - fraction of AUC extrapolated to infinity

λ_z - apparent terminal elimination rate constant

C_{max} - maximum observed plasma drug concentration

T_{max} - time of maximum plasma drug concentration

C_t - the last measurable (non-zero) plasma concentration

$t_{½}$ - apparent terminal elimination half-life

Statistical methods

General: Study results were summarized in tabular format by stage/treatment with descriptive statistics for all assessments in Stage 1 and for subject disposition, demographics, AEs and PK results in Stage 3.

All study results were reported in subject listings for Stage 1 and Stage 3. There was no imputation of missing data.

Demographics: For quantitative variables (e.g., age, height, weight, BMI, and body surface area [BSA]), summary statistics (number [n], mean, standard deviation [SD], minimum, median, and maximum) were presented by treatment sequence for all subjects in the safety population. For the qualitative variables (e.g., sex, race, and ethnicity), results were summarized for all subjects in the safety population as counts and percentages. Individual demographic information for the safety population was displayed in subject listings.

Safety and Tolerability: The original terms used to report AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0. An overall summary table for all treatment-emergent AEs was presented by treatment group. In addition, a frequency table was presented by treatment group for all treatment-emergent AEs by system organ class and preferred term for the safety population.

For clinical laboratory results, summary statistics (n, mean, SD, minimum, median, and maximum) and change from baseline (values obtained at Period 1, Day -1) were presented by treatment sequence for Stage 1. Individual subject data were displayed in subject listings for Stage 1 and Stage 3.

Summary statistics, change from baseline results and individual subject listings were also presented for vital signs and quantitative ECG variables for Stage 1. Vital signs and ECG parameters were presented in subject listings for Stage 1 and Stage 3.

Pharmacokinetics: Plasma cysteamine concentrations through 24 hours were summarized by descriptive statistics by treatment group using the following metrics: n, arithmetic mean, SD, percent coefficient of variation [%CV], minimum, median, and maximum. Cysteamine PK parameters were summarized using the following metrics: n, arithmetic mean, SD, %CV, minimum, median, maximum, geometric mean and %CV for the geometric mean. All PK data were displayed in subject listings.

Statistical analyses (including bioequivalence testing) were planned for Stage 1 and Stage 2. As described above in the Study Methodology section, PK parameters could not be accurately estimated following Stage 1 due to low blood concentrations of cysteamine; therefore, Stage 2 was not conducted, and the protocol was amended to include Stage 3 followed by study termination. The planned bioequivalence analysis was not conducted.

Results

Pharmacokinetic Results

- Datasets Analyzed

Concentration data for 16 of the 18 subjects who received active drug was included in the PK analysis. Subject 116 withdrew consent following Period 1 of Stage 1 and Subject 117 had only 1 quantifiable concentration during Period 1 of Stage 1. Therefore, these 2 subjects were not included in the summarization of Stage 1 results for opened versus intact capsules. Due to low cysteamine concentrations, λz was estimable for only 4 of 16 subjects for the opened capsules treatment and 3 of 16 subjects for the intact capsules treatment. Therefore, λz, t½, fext and $AUC_{(0\text{-}inf)}$ were not estimated or reported for the Stage 1, intact versus opened capsules comparison.

Pharmacokinetic data for all 4 of the subjects who returned for Stage 3 (fasted, intact capsules) were included in the summarization of PK parameters for intact capsules given under fed and fasted conditions. However, PK parameters for Stage 1 for the corresponding 4 subjects was available for only 3 of the 4 subjects, since Subject 117 had only 1 quantifiable concentration during the intact capsule treatment period of Stage 1. Based upon the established criteria for estimation of λz (greater than 2 concentration values in the terminal portion of the curve and Rsquare >0.80), λz was estimable for the 4 subjects after receiving the intact capsules under fasted conditions (Stage 3) and was estimable in 3 of the 4 subjects (#108, #114, and #118) after receiving the intact capsules under fed conditions (Stage 1). Therefore λz, t½, fext and $AUC_{(0\text{-}inf)}$ were estimated and reported for the 4 subjects in Stage 3, and 3 subjects from Stage 1.

- Plasma Cysteamine PK parameters and concentrations

Plasma cysteamine PK parameters after a single 600 mg dose of RP103 intact or opened capsules given with food (Stage 1) are summarized in Table 2 below. The average peak concentration was attained at approximately 6.0 hours after dosing for both Stage 1 treatments. However, less than 2/3 of the total number of subjects in the PK population had detectable concentrations prior to 2.0 hours and after 8.0 hours for the opened capsules treatment. For the intact capsules treatment, less than 2/3 of the subjects had detectable concentrations prior to 6.0 hours and after 12.0 hours. Overall, approximately 40% of the concentrations between 0.5 and 12 hours were below the limit of quantitation of the pharmacokinetic assay (BLQ) for the opened capsules treatment and 72% were BLQ for the intact capsules treatment. For the intact capsules treatment, the majority of subjects did not have detectable levels of cysteamine until 6 hours after dosing, whereas more than half the subjects in the opened capsules treatment had detectable concentrations of cysteamine within 1 hour of dosing.

Table 2. Arithmetic Mean (SD) Plasma Cysteamine Pharmacokinetic Parameters in 16 Fed Healthy Subjects following a Single 600 mg Dose of RP103 Opened or Intact Capsules

	RP103 Open Capsules Fed Subjects	**RP103 Intact Capsules Fed Subjects**
	Arithmetic mean (SD)	**Arithmetic mean (SD)**
$AUC_{(0\text{-}\infty)}$ (hr·ng/mL)	2612 (1095)	2784 (1169)
C_{max} (ng/mL)	706 (355)	801 (513)
T_{max}* (hr)	6.00 (1.50 – 10.0)	6.00 (4.00 – 10.0)

	RP103 Open Capsules Fed Subjects	RP103 Intact Capsules Fed Subjects
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity	
C_{max}	maximum plasma concentration	
T_{max}	time for maximum concentration (* median, range)	

A comparison of PK parameters obtained in the subset of 4 subjects who received the intact capsules treatment in fed and fasted states (Table 3) showed more rapid drug absorption under fasted conditions (median Tmax of 3.25 hours versus 6.0 hours for fasted versus fed treatment, respectively).

The average peak concentration was attained at 3.0 hours and 6.0 hours, respectively, after dosing the intact capsules while fasted and fed. Two of 4 subjects had quantifiable concentrations from 1.0 through 12.0 hours and the remaining 2 subjects had quantifiable concentrations from 1.5 through 8.0 hours and 1.0 through 10.0 hours for the fasted capsules treatment.

Table 3. Arithmetic Mean (SD) Plasma Cysteamine Pharmacokinetic Parameters in a Subset of 4 Healthy Subjects following a Single 600 mg Dose of RP103 Intact Capsules Given Under Fed and Fasted Conditions

	RP103 Intact Capsulesb [Fed Subjects (from Stage 1)]	RP103 Intact Capsules [Fasted Subjects (Stage 3)]
	Arithmetic mean (SD)	**Arithmetic mean (SD)**
$AUC_{(0-t)}$ (hr·ng/mL)	3679 (1105)	5831 (1912)
$AUC_{(0-\infty)}$ (hr·ng/mL)	4036 (1186)	6122 (2020)
fext (%)	9.04 (2.02)	4.68 (0.355)
C_{max} (ng/mL)	1163 (533)	2058 (502)
T_{max}* (hr)	6.00 (4.00 – 6.00)	3.25 (3.00 – 4.00)
t ½ (hr)	2.29 (0.331)	2.31 (0.856)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours	
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity	
fext	fraction of AUC extrapolated to infinity	
C_{max}	maximum plasma concentration	
T_{max}	time for maximum concentration (* median, range)	
t ½	apparent terminal elimination half-life	

- Conclusions

Inadequate plasma cysteamine exposure after administration of RP103 with a high-fat meal precluded bioequivalence testing of the intact versus opened capsules treatments.

Based upon a subset of 4 subjects who received RP103 under fasted and fed conditions, cysteamine exposure was significantly greater in the fasted than fed state.

- **Protocol Number**: RP103-05

Study Title: A Randomized, Open-Label, 2-way Crossover, Single-Dose, Sequential Design Study to Evaluate the Bioequivalence of Two Different Modes of Administration of Cysteamine Bitartrate Delayed-release Capsules (RP103) Following a 600 mg Dose in Healthy Subjects

Methods

Study design

Investigator and Study Center: Shanthini Daniel, MD, Jasper Clinic, Inc. Kalamazoo, MI

Objectives: 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 [Treatment B]

and

2) content of opened delayed-release capsules [Treatment A].

An additional exploratory parallel-group meal delay arm of the study evaluated the pharmacokinetics (PK) of both modes of administration in a fasted state; then followed by a meal given 30 minutes and 2 hours after the dose.

Methodology: This was a single center, open-label, randomized, 2-period, 2-sequence, crossover bioequivalence (BE) study followed by an additional exploratory parallel-group meal delay period. A 2 Stage sequential design that incorporated an interim BE analysis after completion of Stage 1 was planned. If bioequivalence or non-bioequivalence was concluded at that time, then the study would have been stopped following the exploratory parallel-group meal delay period. If bioequivalence was not concluded at Stage 1, but the observed ratios for area under the concentration-time curve from time 0 to infinity ($AUC_{(0\text{-}inf)}$), area under the concentration–time curve from 0 to t, the time of the last measurable concentration ($AUC_{(0\text{-}t)}$), or maximum observed plasma drug concentration (C_{max}) were within 0.80 to 1.25, the study would proceed to Stage 2 with 20 additional subjects.

Interim analysis after Stage 1 showed bioequivalence, with the 94.12% confidence intervals for the ratio of the least-squares means for $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$ and C_{max} all within 0.80 to 1.25. Therefore Stage 2 was cancelled and the study was stopped.

Treatment A: The contents of opened 8 x 75 mg delayed-release capsules, microspheronized beads, administered mixed with applesauce.

Treatment B: 8 x 75 mg intact delayed-release capsules swallowed whole, administered with applesauce. The single oral cysteamine dose in Periods 1 and 2 was 600 mg, administered in a fasted state. Treatment sequence was randomized so that subjects received either Treatment A or Treatment B administered in a fasted state on Day 1 of Periods 1 and 2.

During Period 3, the same single oral cysteamine dose was 600 mg. Subjects were randomized to 1 of 4 treatment/meal delay schedules:

AM1: Treatment A (Opened Capsules); Meal 1 (30 minutes post-dose)

AM2: Treatment A (Opened Capsules); Meal 2 (2 hours post-dose)

BM1: Treatment B (Intact Capsules); Meal 1 (30 minutes post-dose)

BM2: Treatment B (Intact Capsules); Meal 2 (2 hours post-dose)

There was a washout of at least 3 days, but no more than 7 days between all doses.

Duration of Treatment: Subject screening procedures were performed within 28 days of administration of study drug. Treatments A and B were administered in a randomized crossover fashion in 2 study periods. Each subject received a single 600 mg dose of study drug (RP103) on Day 1 of Period 1, followed by a 4-day washout, and then a second single 600 mg dose of study drug (RP103) was given on Day 1 of Period 2.

After another four-day washout, subjects were re-admitted for Period 3. During Period 3, each subject received a single 600 mg dose of study drug (RP103) on Day 1 following randomization to 1 of 4 capsule treatment/meal delay schedules. Study exit procedures were performed at the Follow-up visit 7±2 days after the last dosing or within 14 days after the last participation of the subject in the study. The total duration of study participation was approximately 47 days.

Test and reference products

Drug Product: RP103, Cysteamine bitartrate (equivalent to 75 mg cysteamine free base) delayed release capsules containing microspheronized beads Manufactured by Patheon Pharmaceuticals, Inc., Cincinnati, Ohio for Raptor Pharmaceuticals Inc.

Population studied

Up to 40 healthy volunteers, male or female, smokers or nonsmokers were planned for inclusion into the study. Nineteen of 20 subjects completed the Stage 1, crossover BE Periods 1 and 2. Seventeen subjects completed the Stage 1, Period 3 parallel-group meal delay portion of the study. Stage 2 was to include 20 additional subjects following the same study schedule and treatment regimen as Stage 1; however Stage 2 was not conducted because bioequivalence was concluded after Stage 1.

Analytical methods

Plasma samples containing sodium heparin as the anticoagulant were analyzed for cysteamine using protein precipitation extraction with acetonitrile and liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The analytical method was developed and validated), and has a calibration range of 10.0 to 2500 ng/mL.

Pharmacokinetic variables

Blood samples for measurement of cysteamine in plasma were drawn relative to each single dose as follows: 0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18 and 24 hours after study drug administration.

Samples were collected into chilled collection tubes containing sodium heparin, and were stored on wet ice until centrifuged within 30 minutes of collection. Tubes were centrifuged at 2000g and 4ºC for 10 minutes. The resultant plasma was split equally into 2 aliquots and transferred into chilled 1.0 mL polypropylene CryoTubes. All CryoTubes were transferred to the freezer within 1 hour of collection and stored at approximately -70ºC until shipment. Frozen aliquots were shipped under dry ice for analysis.

The following PK parameters were estimated from the plasma concentration-time profiles based upon actual collections times:

$AUC_{(0-t)}$ - area under the concentration-time curve from time 0 to t, the time of the last measurable concentration

$AUC_{(0-inf)}$ - area under the concentration-time curve from time 0 to infinity

F_{ext} - fraction of AUC extrapolated to infinity

λ_z - apparent terminal elimination rate constant

C_{max} - maximum observed plasma drug concentration

T_{max} - time of maximum plasma drug concentration

C_t - the last measurable (non-zero) plasma concentration

$t_{½}$ - apparent terminal elimination half-life

Statistical methods

General: For the crossover BE portion of the study, results were summarized in tabular format by treatment group or by treatment sequence, unless otherwise specified. For the parallel-group meal delay portion of the study, results were summarized in tabular format by treatment group. All statistical testing performed was two-sided, using a 0.05 level of significance. All study results were reported in subject listings. There was no imputation of missing data.

Demographics: For quantitative variables (e.g., age, height, weight, BMI, and body surface area [BSA]), summary statistics (number [n], mean, standard deviation [SD], minimum, median, and maximum) were presented by treatment sequence group or treatment group the safety population. For the qualitative variables (e.g., sex, race, and ethnicity), results were summarized by treatment sequence group or treatment group as counts and percentages. Individual demographic information for the safety population was displayed in subject listings.

Safety and Tolerability: The original terms used to report AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0. An overall summary table for all treatment-emergent AEs was presented by treatment group. In addition, a frequency table was presented by treatment group for all treatment-emergent AEs by system organ class (SOC) and preferred term for the safety population.

For clinical laboratory results and vital signs, summary statistics (n, mean, SD, minimum, median, and maximum) and change from baseline (values obtained at Period 1, Day -1) were presented by treatment sequence group or treatment group for the safety population. For

quantitative ECG variables, the same results were presented using the Screening ECG as baseline. Individual subject data were displayed in subject listings.

Pharmacokinetics: Plasma cysteamine concentrations through 24 hours were summarized by descriptive statistics by treatment group using the following metrics: n, arithmetic mean, SD, percent coefficient of variation [%CV], minimum, median, and maximum. Cysteamine PK parameters were summarized using the following metrics: n, arithmetic mean, SD, %CV, minimum, median, maximum, geometric mean and %CV for the geometric mean. All PK data were displayed in subject listings.

- Crossover Bioequivalence Periods 1 and 2

In order to preserve the overall type I error of the crossover portion of the trial, analyses were conducted at adjusted significance levels, using a 94.12% confidence interval.

With data from Stage 1, analysis of variance (ANOVA) was performed on untransformed Tmax, λz, and t½ and on ln-transformed AUC(0-t), AUC(0-inf), and Cmax at the alpha level of 0.05. Factors incorporated in the model included: Sequence, Subject (Sequence), Period, and Treatment. The ratio of means (A/B) and 94.12% geometric confidence interval for the ratio of means, based on least-squares means from the ANOVA of the ln-transformed data were calculated for AUC(0-t), AUC(0-inf), and Cmax.

Criteria for average bioequivalence Stage 1 (with data from Stage 1, Periods 1 and 2 only):

1) If the 94.12% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC(0-inf), AUC(0-t), and Cmax were within 0.80 to 1.25, then bioequivalence would have been concluded and the study stopped.

2) If the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC(0-inf), AUC(0-t), or Cmax was outside 0.80 to 1.25, then non-bioequivalence would have been concluded and the study stopped.

3) If bioequivalence was not concluded at Stage 1, but the observed ratios for AUC(0-inf), AUC(0-t), and Cmax were within 0.80 to 1.25, then the study would have proceeded to Stage 2.

- Exploratory Parallel-Group Meal Delay Period 3

For comparison of the fasted vs. fed (meal delay of 30 minutes) and the fasted vs. fed (meal delay of 2 hours), a paired t-test was performed separately for Treatment A and Treatment B on untransformed Tmax, λz, and t½ and on 1n-transformed $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} at the alpha level of 0.05. The 95% geometric confidence interval (CI) of the ratio (fed/fasted) of means, based on least squares means from a paired t-test of the 1n-transformed $AUC_{(0-inf)}$, $AUC_{(0-t)}$, and C_{max}, were displayed separately for Treatment A and Treatment B. All statistical testing performed was two-sided, using a 0.05 level of significance.

Results

Pharmacokinetic Results

- Datasets Analyzed

Concentration data for 19 of 20 subjects who received active drug was included in the BE analysis in Periods 1 and 2. Subject 101 was excluded from the study following Period 1; therefore associated concentration and PK parameter data for this subject was not included in the summarization and BE analysis of Stage 1 results for opened versus intact capsules.

Pharmacokinetic data for all 17 of the subjects who returned for the exploratory parallel-group meal delay portion of the study (Period 3) was included in the summarization of RP103 plasma concentrations and PK parameters for opened and intact capsules with a meal delay of 30 minutes or 2 hours. The number of subjects included and reported per treatment group was as follows: 3 subjects in the opened capsule/30-minute meal delay (AM1), 4 subjects in opened capsule/2-hour meal delay (AM2), 5 subjects in intact capsule/30-minute meal delay (BM1), and 5 subjects in the intact capsule/2-hour meal delay (BM2).

- Plasma Cysteamine PK Parameters and Concentrations, Crossover Bioequivalence Periods 1 and 2

Plasma cysteamine PK parameters in healthy fasted subjects after receiving a single 600 mg dose of RP103 opened or intact capsules in a crossover manner are summarized in Table 4 below. The average peak concentration was attained at approximately 3.0 hours after dosing for both treatments. All subjects had detectable concentrations over the 24-hour sampling period for both treatments.

Table 4. Arithmetic Mean (SD) Plasma Cysteamine Pharmacokinetic Parameters in 19 Fasted Healthy Subjects following a Single 600 mg Dose of RP103 Opened or Intact Capsules

	RP103 Opened Capsules Treatment A	**RP103 Intact Capsules Treatment B**
	Arithmetic mean (SD)	**Arithmetic mean (SD)**
$AUC_{(0\text{-}t)}$ (hr·ng/mL)	7965 (1984)	7795 (1779)
$AUC_{(0\text{-}\infty)}$ (hr·ng/mL)	8197 (2049)	8039 (1848)
fext (%)	2.82 (0.552)	2.99 (0.609)
C_{max} (ng/mL)	2316 (718)	2268 (576)
T_{max}* (hr)	3.00 (1.50 – 6.00)	3.00 (2.00 – 4.00)
t ½ (hr)	6.06 (0.970)	6.08 (0.840)

$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from time zero to infinity
fext	fraction of AUC extrapolated to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)
t ½	apparent terminal elimination half-life

- Bioequivalence Results for Opened versus Intact Capsule Treatment

The results of statistical testing for bioequivalence using 94.12% confidence intervals for the least-squares geometric mean ratios (opened/intact) are summarized in Table 5.

Table 5. Statistical Analysis for Bioequivalence Comparison of Opened (Treatment A) to Intact (Treatment B) RP103 Capsules

	Geometric Mean Ratio (A/B)	**94.12% Confidence Interval for Ratio of Least Squares Mean**
Geometric AUC(0-t)	1.012	0.959–1.069

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

All estimates of the ratios for the parameters $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} 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. There were no significant sequence or period effects observed.

- Plasma Cysteamine Concentrations and Pharmacokinetic Parameters, Parallel-Group Meal Delay Period 3

Reduced plasma concentrations were observed for both the opened and intact capsule treatments when a meal was administered 30 minutes following drug administration, compared to fasted conditions. Similar average concentration-time profiles were observed between the 2-hr meal delay, compared with fasted conditions for both capsule treatments.

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 C_{max} between the 2 hour meal, compared with fasted conditions for both the opened and 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 treatment groups.

- Conclusions

RP103 intact and opened capsules (contents combined with a small amount of applesauce) are bioequivalent after administration of a single 600-mg dose.

When RP103 was given 30 minutes after a standard meal as either opened or intact capsules, bioavailability of cysteamine appeared to be decreased. This finding is consistent with results of Study RP103-02 in which consumption of a high-fat meal just prior to dosing with RP103 capsules resulted in reduced cysteamine absorption compared to dosing in the fasted state6. No difference in cysteamine bioavailability was apparent when the meal was taken 2 hours after RP103 administration (opened or intact capsules), as compared with bioavailability in the fasted state (meal given 4 hours after RP103 administration).

- **Protocol Number**: RP103-06

Study Title: A Randomized, Open-Label, 2-way Crossover, Single-Dose Study to Evaluate the Bioequivalence of Two Different Modes of Administration of Cysteamine Bitartrate Delayed-release Capsules (RP103) Following a 600 mg Dose in Fasted Healthy Volunteers

Methods

Study design

Investigator and Study Center: Shanthini Daniel, MD, Jasper Clinical Research and Development, Inc., 526 Jasper Street, Kalamazoo, MI 49007

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

1) intact delayed release capsules [Treatment B]

and

2) content of opened delayed-release capsules [Treatment A].

Methodology: This was a single-center, open-label, randomized, 2-period, 2-way crossover study to evaluate the bioequivalence (BE) of a 600 mg dose of cysteamine bitartrate delayed-release capsules (RP103) given as open capsules mixed with applesauce or intact capsules taken with orange juice to healthy subjects under fasted conditions.

Treatment A: The contents of opened 8 x 75 mg delayed-release capsules, microspheronized beads, administered mixed with applesauce and swallowed with orange juice.

Treatment B: 8 x 75 mg intact delayed-release capsules swallowed whole, administered with orange juice.

The single oral cysteamine dose was 600 mg, administered in a fasted state. Treatment sequence was randomized so that subjects received either Treatment A or Treatment B on Day 1 of Periods 1 and 2.

There was a washout of 5 days between doses.

Duration of Treatment: Subject screening procedures were performed within 28 days of administration of study drug.

Treatments A and B were administered in a randomized crossover fashion in 2 study periods. Each subject received a single 600 mg dose of study drug (RP103) on Day 1 of Period 1, followed by a 5-day washout, and then a second single 600 mg dose of study drug (RP103) was given on Day 1 of Period 2.

Study exit procedures were performed at the Follow-up visit 7±2 days after the last dosing or within 14 days after the last participation

Test and reference products

Drug Product: RP103, Cysteamine bitartrate (equivalent to 75 mg cysteamine free base) delayed release capsules containing microspheronized beads [Manufactured and distributed by Patheon Pharmaceuticals, Inc., Cincinnati, Ohio for Raptor Pharmaceuticals Inc. (Lot 3095307).

Population studied

Twenty healthy adults, male or female, smokers or nonsmokers were planned for inclusion into the study. One subject withdrew; therefore, 19 of 20 subjects completed the entire study.

Analytical methods

Plasma samples containing sodium heparin as the anticoagulant were analyzed for cysteamine using protein precipitation extraction with acetonitrile and liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The analytical method was developed and validated and has a calibration range of 10.0 to 2500 ng/mL.

Pharmacokinetic variables

Blood samples for measurement of cysteamine in plasma were drawn relative to each single dose as follows: 0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18 and 24 hours after study drug administration.

Samples were collected into chilled collection tubes containing sodium heparin, and were stored on wet ice until centrifuged within 30 minutes of collection. Tubes were centrifuged at 2000g and 4ºC for 10 minutes. The resultant plasma was split equally into 2 aliquots and transferred into chilled 1.0 mL polypropylene CryoTubes. All CryoTubes were transferred to the freezer within 1 hour of collection and stored at approximately -70ºC until shipment. Frozen aliquots were shipped under dry ice for analysis.

The following pharmacokinetic (PK) parameters were estimated from the plasma concentration-time profiles based upon actual collections times:

$AUC_{(0-t)}$ - area under the concentration-time curve from time 0 to t, the time of the last measurable concentration

$AUC_{(0-inf)}$ - area under the concentration-time curve from time 0 to infinity

F_{ext} - fraction of AUC extrapolated to infinity

λ_z - apparent terminal elimination rate constant

C_{max} - maximum observed plasma drug concentration

T_{max} - time of maximum plasma drug concentration

C_t - the last measurable (non-zero) plasma concentration

$t_{½}$ - apparent terminal elimination half-life

Statistical methods

General: Results were summarized in tabular format by treatment group or by treatment sequence unless otherwise specified. All statistical testing performed was two-sided, using a 0.01 level of significance. All study results were reported in subject listings. There was no imputation of missing data.

Demographics: For quantitative variables (age, height, weight, BMI, and body surface area [BSA]), summary statistics (number [n], mean, standard deviation [SD], minimum, median and maximum) were presented by treatment sequence group for the safety population. For the qualitative variables (sex, race and ethnicity), results were summarized by treatment sequence group as counts and percentages for the safety population. Individual demographic information was displayed in subject listings.

Safety and Tolerability: The safety population was defined as all subjects who signed the study-specific informed consent document and received at least 1 dose of study drug. The original terms used to report AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0. An overall summary table for all treatment-emergent AEs was presented by treatment group. In addition, a frequency table was presented by treatment group for all treatment-emergent AEs by system organ class (SOC) and preferred term for the safety population.

For clinical laboratory results and vital signs, summary statistics (n, mean, SD, minimum, median and maximum) and change from baseline were presented by treatment sequence group for the safety population. The values obtained at Period 1, Day -1 were considered the baseline, except for temperature, which was obtained at Day 1 predose. For quantitative ECG variables, the same results were presented using the Screening ECG as baseline. Individual subject data were displayed in subject listings.

Pharmacokinetics: The PK population was defined as all randomized subjects who received study drug and for whom the PK profile could be adequately characterized. Plasma cysteamine concentrations through 24 hours were summarized by descriptive statistics by treatment group using the following metrics: n, arithmetic mean, SD, percent coefficient of variation [%CV], minimum, median and maximum. Cysteamine PK parameters were summarized using the following metrics: n, arithmetic mean, SD, %CV, minimum, median, maximum, geometric mean and %CV for the geometric mean. All PK data were displayed in subject listings.

Analysis of variance (ANOVA) was performed on untransformed λz, and t½ and on ln-transformed $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} at the alpha level of 0.01. Factors incorporated in the model included:

- Sequence, Subject (Sequence), Period and Treatment.

The ratio of means (Treatment A/Treatment B) and 90% geometric confidence interval (CI) for the ratio of means, based on least-squares means from the ANOVA of the ln-transformed data were calculated for $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max}.

Comparison of T_{max} values between treatments were based on nonparametric methods. The Hodges-Lehmann method was performed to calculate the point estimate and 90% CI for the median differences of T_{max} values. Statistically significant difference in Tmax was to be concluded if the 90% CI did not contain 0.

- Criteria for average bioequivalence

If the 90% geometric CIs of the ratio (Treatment A/Treatment B) of least-squares means from the ANOVA of the ln-transformed $AUC_{(0-inf)}$, $AUC_{(0-t)}$ and C_{max} were within 80.00% to 125.00%, then bioequivalence would be concluded.

Results

Pharmacokinetic Results

- Datasets Analyzed

Concentration data for 19 of 20 subjects who received active drug was included in the BE analysis. Subject 106 withdrew from the study following Period 1; therefore associated concentration and PK parameter data for this subject were not included in the summarization and BE analysis.

- Plasma Cysteamine PK parameters and Concentrations

Plasma cysteamine PK parameters in healthy fasted subjects after receiving a single 600 mg dose of RP103 opened or intact capsules in a crossover manner are summarized in Table 9. Mean (±SD) plasma cysteamine concentrations in healthy fasted subjects after receiving a single 600 mg dose of RP103 opened or intact capsules in a crossover manner are shown in Figure 1, below. The average peak concentration was attained at approximately 4.0 hours after dosing for opened capsules and 3.5 hours after dosing for intact capsules. All subjects had detectable concentrations (>10 ng/mL) over the 24-hour sampling period for both treatments.

Table 6. Arithmetic Mean (SD) Plasma Cysteamine Pharmacokinetic Parameters in 19 Fasted Healthy Subjects following a Single 600 mg Dose of RP103 Opened or Intact Capsules

	RP103 Opened Capsules Treatment A	**RP103 Intact Capsules Treatment B**
	Arithmetic mean (SD)	**Arithmetic mean (SD)**
$AUC_{(0\text{-}t)}$ (hr·ng/mL)	6795 (1868)	6868 (1695)
$AUC_{(0\text{-}\infty)}$ (hr·ng/mL)	7001 (1918)	7087 (1757)
fext (%)	2.96 (0.583)	3.07 (0.682)
C_{max} (ng/mL)	2074 (615)	2157 (415)
T_{max}* (hr)	3.50 (1.00 – 4.00)	3.50 (2.00 – 4.00)
t ½ (hr)	5.78 (0.671)	5.86 (0.817)

$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from time zero to infinity
fext	fraction of AUC extrapolated to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)
t ½	apparent terminal elimination half-life

- Statistical Comparison of Opened Versus Intact Capsule Treatments

The results of statistical testing for bioequivalence using 90% CIs for the least-squares geometric mean ratios (opened/intact) are summarized in Table 7

Table 7. Statistical Analysis for Bioequivalence Comparison of Opened (Treatment A) to Intact (Treatment B) RP103 Capsules

	Geometric Mean Ratio (A/B)	**90% Confidence Interval for Ratio of Least-Squares Means**
Geometric AUC(0-t)	0.978	0.913–1.047

	Geometric Mean Ratio (A/B)	90% Confidence Interval for Ratio of Least-Squares Means
Geometric AUC(0-inf)	0.976	0.911–1.046
Geometric Cmax	0.922	0.816–1.043

Estimates of the geometric least squares mean ratios for the parameters $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} indicated minimal differences (<8%) between treatments. The 90% CIs for all comparisons were within the acceptance range for bioequivalence of 80.00 - 125.00%. There were no significant period or sequence effects observed (p>0.23 and p>0.34, respectively).

- Comparison of cysteamine PK between fed and fasted healthy volunteers across BE studies (RP103-02, RP103-05 and RP103-06)

Study RP103-02, Study RP103-05 and Study RP103-06 were all performed in healthy volunteers with a single dose of 600 mg RP103. The assessment of the food effect on the PK of cysteamine after a single dose of RP103 is strictly equivalent, with dose normalized or non-dose normalized data.

Table 8. Pharmacokinetic parameters of plasma cysteamine after a 600 mg single dose of RP103 in fed and fasted healthy volunteers

Study	RP103-02			RP103-05						RP103-06	
Fed vs. Fasted	Fed before		Fasted	Fasted		Fed after				Fasted	
Food Delay	30 min					30 m	2 h	30 m	2 h		
	02-A	02-B	02-C	05-A	05-B	05-C	05-D	05-E	05-F	06-A	06-B
C_{max}	0.68 ± 0.09	0.84 ± 0.13	2.06 ± 0.25	2.26 ± 0.16	2.27 ± 0.13	1.18 ± 0.31	3.18 ± 0.11	1.60 ± 0.38	2.44 ± 0.23	2.10 ± 0.13	2.16 ± 0.09
AUC_{all}	168 ± 18	198 ± 23	376 ± 63	493 ± 27	487 ± 25	277 ± 56	575 ± 21	356 ± 68	516 ± 51	429 ± 26	433 ± 24
T_{max}	345 ± 35	440 ± 35	202 ± 14	190 ± 14	194 ± 9	200 ± 140	172 ± 7	282 ± 76	186 ± 15	193 ± 12	202 ± 8

- **Protocol Number**: RP103-HLTA-009

Study Title: An Open-Label, Single-Dose Study to Evaluate the Bioequivalence of Cysteamine Bitartrate Delayed-release Capsules (RP103) Following a 600 mg Dose Before and During Treatment with Omeprazole, a Proton Pump Inhibitor (PPI)

Methods

Study design

Investigator and Study Center: Otto I. Linet, MD, PhD Jasper Clinic, Inc., 526 Jasper Street, Kalamazoo, MI 49007

Objectives: The objective of this study was to compare the rate and extent of absorption of cysteamine bitartrate delayed-release capsules (RP103) following a single dose of 600 mg

administered under two different fasted conditions: taken alone and taken with the fifth consecutive daily dose of the proton pump inhibitor (PPI), omeprazole.

Methodology: This was a single-center, open-label, 2-period, sequential design study to evaluate the bioequivalence (BE) of a 600 mg dose of cysteamine bitartrate delayed-release capsules (RP103) given alone and given with the fifth consecutive daily dose of the proton pump inhibitor, omeprazole. Both treatments were administered under fasting conditions to healthy subjects with 240 mL orange juice. The study included one cohort of 20 volunteers that received the following treatment regimen according to the table below:

Table 9. Treatment for Period/Study Day

Treatment for Period/Study Day					
Period 1	**Period 2**				
Day 1 Treatment A	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6 Treatment B**
RP103 600 mg alone, taken with 240 mL orange juice	Omeprazole 20 mg, taken with 240 mL water	Omeprazole 20 mg, taken with 240 mL water	Omeprazole 20 mg, taken with 240 mL water	Omeprazole 20 mg, taken with 240 mL water	RP103 600 mg and Omeprazole 20 mg, taken with 240 mL orange juice

Dosing of reference and test treatments (RP103 alone, and with the 5th consecutive daily dose of omeprazole) occurred on the morning of Day 1 and Day 6, respectively, beginning at approximately 0900 and was to be as consistent as possible between days for a given subject throughout the study. Subjects were confined to the clinical research unit (CRU) from Day -1 until the morning of Day 2, and again from Day 5 until the morning of Day 7. Subjects were required to return to the clinic to receive omeprazole on an outpatient basis on the morning of Days 3 and 4. Subjects returned to the CRU for omeprazole dosing and admission to the CRU on the morning of Day 5. Subjects underwent a drug and alcohol screen and serum pregnancy test (females), and their eligibility was verified (including laboratory assessments) upon each admission.

Blood samples for the determination of cysteamine plasma levels were drawn during the 24 hours after each RP103 single dose of study drug (on Days 1 and 6). All subjects participated in a Follow-up visit 5 to 9 days after receiving their last dose of study drug.

Period 1: 8 x 75 mg delayed-release intact RP103 capsules (total dose of 600 mg cysteamine free base) administered with orange juice on Day 1 (Treatment A).

Period 2: 1 x 20 mg omeprazole capsule, each morning for 5 days (Days 2, 3, 4, 5 and 6). 8 x 75 mg delayed-release intact RP103 capsules (total dose of 600 mg cysteamine free base) administered with orange juice, taken with morning dose of 1 x 20 mg omeprazole capsule on Day 6 (Treatment B).

Subjects swallowed the capsules intact within 2 minutes from the start of dosing. All subjects ingested Treatment A (Day 1) and Treatment B (Day 6) with 240 mL of orange juice. Subjects

ingested 240 mL of water along with the 20 mg dose of omeprazole on the mornings of Days 2, 3, 4, and 5.

Duration of Treatment: Subject screening procedures were performed within 14 days of administration of study drug on Day 1. Treatments A and B were administered in a sequential fashion with all subjects receiving Treatment A on Day 1/Period 1 and Treatment B on Day 6/Period 2. Each subject received a single 600 mg dose of study drug (RP103) on Day 1/Period 1. Period 2 began on Day 2 and all subjects received a single 20 mg dose of omeprazole on Days 2, 3, 4, 5, and 6. A second single 600 mg dose of study drug (RP103) was given on Day 6/Period 2 along with the morning dose of omeprazole 20 mg. Study exit procedures were performed 7±2 days after the last dosing or within 14 days after the last participation of the subject in the study. The total duration of study participation was no more than 28 days including the screening period.

Test and reference products

Drug Products:

- RP103, 75 mg delayed- release capsules (cysteamine bitartrate, dose expressed as cysteamine free base) containing microspheronized beads. RP103 capsules were manufactured and distributed by Patheon Pharmaceuticals, Inc., Cincinnati, Ohio for Raptor Pharmaceuticals Inc. (Lot 3099573).

- Prilosec (Omeprazole), 20 mg capsules were manufactured for Astra Zeneca LP by Merck Sharp and Dohme Corporation

Population studied

Twenty healthy adults, male or female, smokers or nonsmokers, were planned for inclusion into the study. All 20 subjects completed the entire study.

Analytical methods

Plasma samples containing sodium heparin as the anticoagulant were analyzed for cysteamine using protein precipitation extraction with acetonitrile, and liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The analytical method was developed and validated and has a calibration range of 10.0 to 2500 ng/mL.

Pharmacokinetic variables

Blood samples for measurement of cysteamine in plasma were drawn relative to each RP103 single dose as follows: 0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18 and 24 hours after study drug administration.

Samples were collected into chilled collection tubes containing sodium heparin, and were stored on wet ice until centrifuged within 30 minutes of collection. Tubes were centrifuged at 2000g and 4ºC for 10 minutes. The resultant plasma was split equally into 2 aliquots and transferred into chilled 2.0 mL polypropylene Sarstedt vials. All Sarstedt vials were transferred

to the freezer within 1 hour of collection and stored at approximately -70ºC until shipment. Frozen aliquots were shipped under dry ice for analysis.

The following pharmacokinetic (PK) parameters were estimated from the plasma concentration-time profiles based upon actual collections times:

$AUC_{(0-t)}$ - area under the concentration-time curve from time 0 to t, the time of the last measurable concentration

$AUC_{(0-inf)}$ - area under the concentration-time curve from time 0 to infinity

F_{ext} - fraction of AUC extrapolated to infinity

λ_z - apparent terminal elimination rate constant

C_{max} - maximum observed plasma drug concentration

T_{max} - time of maximum plasma drug concentration

C_t - the last measurable (non-zero) plasma concentration

$t_{½}$ - apparent terminal elimination half-life

Statistical methods

General: Results were summarized in tabular format by visit unless otherwise specified. All statistical testing performed was two-sided, using a 0.01 level of significance. All study results were reported in subject listings. There was no imputation of missing data.

Demographics: For quantitative variables (age, height, weight, BMI, and body surface area [BSA]), summary statistics (number [n], mean, standard deviation [SD], minimum, median and maximum) were presented for the safety population. For the qualitative variables (sex, race and ethnicity), results were summarized as counts and percentages for the safety population. Individual demographic information was displayed in subject listings.

Safety and Tolerability: The safety population was defined as all subjects who signed the study-specific informed consent document and received at least 1 dose of study drug. The original terms used to report AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0. An overall summary table for all treatment-emergent AEs was presented by treatment group. In addition, a frequency table was presented by treatment group for all treatment-emergent AEs by system organ class (SOC) and preferred term for the safety population.

For clinical laboratory results and vital signs, summary statistics (n, mean, SD, minimum, median and maximum) and change from baseline were presented for the safety population. The values obtained on Day -1 were considered the baseline for clinical laboratory results and the values obtained on Day 1 pre-dose were the baseline for vital signs. For quantitative ECG variables, the same summary statistics were presented using the Screening ECG as baseline. Individual subject data were displayed in subject listings.

Pharmacokinetics: The PK population was defined as all randomized subjects who received study drug and for whom the PK profile could be adequately characterized. Plasma cysteamine concentrations through 24 hours were summarized by descriptive statistics by treatment

group using the following metrics: n, arithmetic mean, SD, percent coefficient of variation [%CV], minimum, median and maximum. Cysteamine PK parameters were summarized using the following metrics: n, arithmetic mean, SD, %CV, minimum, median, maximum, geometric mean and %CV for the geometric mean. All PK data were displayed in subject listings.

A two-sided paired t-test was performed on untransformed λz and t½ and on ln-transformed $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} at the alpha level of 0.01. The ratio of means (Treatment B/Treatment A) and 90% geometric confidence interval (CI) for the ratio of means, based on a paired t-test on the ln-transformed data, were calculated for $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max}.

Comparison of T_{max} values between treatments were based on nonparametric methods. The Hodges-Lehmann method was performed to calculate the point estimate and 90% CI for the median differences of T_{max} values. A statistically significant difference in T_{max} was to be concluded if the 90% CI did not contain 0.

- Statistical criteria for average bioequivalence

If the 90% geometric CIs of the ratio (Treatment B/Treatment A), based on a paired t-test of the lntransformed $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} were within 80.00% to 125.00%, then bioequivalence would be concluded.

Results

Pharmacokinetic Results

- Datasets Analyzed

Concentration data for 20 of 20 subjects who received study drug were included in the BE analysis.

- Plasma Cysteamine Concentrations

Plasma cysteamine PK parameters in healthy fasted subjects after receiving a single 600 mg dose of RP103 alone and with the fifth consecutive daily 20 mg dose of omeprazole are summarized by treatment in Table 10. The average peak cysteamine concentration (C_{max}) was attained at approximately 3.5 hours after dosing RP103 capsules alone or with omeprazole. All subjects had detectable concentrations (>10 ng/mL) over the 24-hour sampling period for both treatments.

Table 10. Arithmetic Mean (SD) Plasma Cysteamine Pharmacokinetic Parameters in 20 Fasted Healthy Subjects Following a Single Oral 600 mg Dose of RP103 Capsules Given Alone and With the Fifth Consecutive Daily 20 mg Dose of Omeprazole Capsules

	RP103 Alone (Day 1) Treatment A	**RP103 + Omeprazole (Day 6) Treatment B**
	Arithmetic mean (SD)	**Arithmetic mean (SD)**
$AUC_{(0-t)}$ (hr·ng/mL)	7390 (1852)	7486 (1551)
$AUC_{(0-\infty)}$ (hr·ng/mL)	7607 (1924)	7708 (1621)
fext (%)	2.79 (0.635)	2.81 (0.559)

	RP103 Alone (Day 1) Treatment A	RP103 + Omeprazole (Day 6) Treatment B
C_{max} (ng/mL)	2341 (608)	2454 (637)
T_{max}* (hr)	3.50 (1.00 – 4.00)	3.50 (1.00 – 4.00)
t ½ (hr)	5.82 (0.659)	5.67 (0.487)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours	
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity	
fext	fraction of AUC extrapolated to infinity	
C_{max}	maximum plasma concentration	
T_{max}	time for maximum concentration (* median, range)	
t ½	apparent terminal elimination half-life	

- Statistical Comparison of RP103 Capsules Given with Omeprazole Capsules to RP103 Capsules Given Alone

The results of statistical testing for bioequivalence using 90% CIs for the least-squares geometric mean ratios (RP103 + Omeprazole / RP103 Alone) are summarized in Table 11.

Table 11. Statistical Analysis for Bioequivalence: Comparison of RP103 Capsules Given with Omeprazole Capsules (Treatment B) to RP103 Capsules Given Alone (Treatment A)

	Geometric Mean Ratio (B/A)	90% Confidence Interval for Ratio of Least-Squares Means
Geometric AUC(0-t)	1.02	0.983–1.060
Geometric AUC(0-inf)	1.02	0.983–1.060
Geometric Cmax	1.04	0.949–1.14

- Conclusions

RP103 intact capsules given alone and with the fifth, consecutive, 20 mg daily dose of omeprazole are bioequivalent after administration of a 600 mg dose with orange juice to healthy fasted subjects.

2.4.3. Pharmacodynamics

No other new pharmacodynamic studies were presented in addition to study RP103-HLTA-009 which evaluated the interaction between RP103 and PPIs (discussed above). No such studies are required for this application.

Mercaptamine is an aminothiol reacting with lysosomes resulting in a thiol-disulfide interchange reaction in where intracellular cystine is converted to cysteine and cysteine-cysteamine mixed disulfide. Both these latter substances can exit the lysosome in patients with cystinosis. The mechanism of action of mercaptamine bitartrate is well established.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of the commercial RP103 has been investigated in seven clinical studies (Table 1). Pharmacokinetics in the patient population and comparison to the reference product

Cystagon is covered in RP103-01 (Phase IIb) and the pivotal study RP103-03 (Phase III) (please see the clinical section for description of studies RP103-01 and RP103-03).

Studies RP103-02, RP103-05 and RP103-06 aimed at establishing bioequivalence between intact cysteamine bitartrate capsules and content of opened capsules sprinkled onto food in healthy volunteers. The study designs were considered adequate to evaluate the bioequivalence of the administration methods. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

Cysteamine concentrations, after RP103 and Cystagon dosing, were analysed using liquid chromatography assays with tandem mass spectrometric detection (LC MS/MS). The pharmacokinetic parameter estimates were calculated, using standard noncompartmental and compartmental methodology, from the plasma concentrations of cysteamine.

The delayed-release PK characteristics of RP103 have been investigated in studies with comparisons to the reference product, Cystagon. The submitted study data supports a consistent delayed-release characteristic of RP103 with a later median T_{max} (3 hours vs. 1 hour) and a longer half-life (4.23 vs. 1.5 hours) of RP103 as compared to immediate release Cystagon indicating absorption rate limited elimination. The relative bioavailability (based on exposure) was investigated in study RP103-01 suggesting a relative bioavailability of 100-140% of RP103 as compared to Cystagon, these data provided the basis for dose selection in the pivotal phase III study RP103-03. In addition, in study RP103-03 a similar 24-hour cysteamine exposure was reached using a daily RP103 dose of 82% of the daily Cystagon dose (please see the clinical section for description of studies RP103-01 and RP103-03).

Throughout the clinical development programme, RP103 and Cystagon have been dosed in both fasted and a number of different fed states (fed 30 min after, fed 2 h after, fed 30 min before, high fat meal, applesauce, chocolate pudding, orange juice).

In general, the studies aiming at describing the effect of food on the PK of cysteamine are small and therefore the results from single studies should be interpreted with caution. However, the data presented by the Applicant indicates in a consistent manner that dosing in a fed state (high-fat, high caloric meal 30 minutes before dosing) reduces cysteamine bioavailability (Study RP103-02: AUC0-t 5.83 h*mg/L (fasted) and 3.68 h*mg/L (fed)).

The same body of data indicates that a meal 2 hours after RP103 administration does not affect the PK of cysteamine. Even though the data covers a number of scenarios, the data is based on small studies and no data on meals had 30 minutes to 2 hours before RP103 administration is available. Therefore, the patients should try to consistently avoid meals and dairy products for at least 1 hour before and 1 hour after PROCYSBI dose.

Bioequivalence between intact RP103 capsules and their content sprinkled on food was studied (RP103-02, RP103-05 and RP103-06) in order to support this administration method for patients unable to swallow capsules. Since a large number of plasma cysteamine concentrations between 0.5 and 12 hours were below the limit of quantitation, (as a result of the food effect) it was not possible to evaluate bioequivalence of the 2 administration methods in study RP103-02. However, since the 90% confidence interval for the ratio of the two formulations was contained within the acceptance interval of 80.00-125.00%, it is considered

that bioequivalence between intact and opened capsules taken with applesauce and/or orange juice has been demonstrated in studies RP103-05 and RP103-06. It can also be concluded that both treatments in study RP103-06 resulted in similar PK parameters as RP103 administered in a fasted state. Consequently, coadministration with either applesauce or orange juice doesn't seem to affect the PK of cysteamine.

Submitted data and Cystagon SmPC indicate that CYP/MAO metabolism and parent cysteamine excretion in urine plays a limited role in the elimination of cysteamine. Further, according to the SmPC of Cystagon the bulk of mercaptamine are excreted as sulphate indicative of not identified metabolism/degradation pathways.

No new data on the distribution of, dose proportionality, time dependency or intra-individual variability have been submitted, which is acceptable. The inter-individual variability of RP103 is high (CV of 40-60%) but similar to the one of Cystagon.

Data on special populations have not been submitted, which is found acceptable given that the disease is identified in childhood and if untreated leads to kidney failure at approximately age of nine, at which point maintenance dialysis or kidney transplant are needed.

Patients receiving RP103 in the Phase 3 efficacy study (RP103-03) were asked to refrain from taking any proton pump inhibitors (PPIs) or gastric acid reducing medications 12 hours prior to their first RP103 dose up to study completion. Literature reports indicate that even a single dose of PPI could lead to an increase of stomach pH up to 6 which led to the concern that the gastro-resistant capsules which are designed to dissolve at pH ≥5.5 might not by-pass the stomach in patients taking PPIs. Therefore the Applicant presented data that show that the concomitant use of medication increasing the gastric pH (antacids) does not influence the delayed release characteristics of RP103 (Study RP103-HLTA-009).

The Applicant has used pharmacokinetic and pharmacodynamic models to describe data from study RP103-03 and RP103-05 including a population PK/PD analysis of the pivotal phase III study RP103-03. However, the CHMP concluded that sufficient model qualification (by assessing predictive performance of the model) has not been provided in order to consider these models to be valid. Therefore, the data from these models have not been taken into consideration in the assessment of the MAA.

2.4.5. Conclusions on clinical pharmacology

Based on the presented bioequivalence studies PROCYSBI gastro resistant capsule is considered bioequivalent with its content mixed with food or liquid. In addition coadministration applesauce or orange juice doesn't affect the PK of cysteamine. Therefore it is recommended that paediatric patients who are at risk of aspiration or not able to swallow can have the hard capsules opened and their content sprinkled on food, liquid or administered through feed-tubes (SmPC section 4.2).

Dosing in a fed state (high-fat, high caloric meal 30 minutes before dosing) reduces cysteamine bioavailability therefore PROCYSBI should not be administered with food rich in fat or proteins (SmPC section 4.2).

The submitted study data supports a consistent delayed-release characteristic of RP103 with a later median T_{max} (3 hours vs. 1 hour) and a longer half-life (4.23 vs. 1.5 hours) of RP103

compared to immediate release Cystagon indicating absorption rate limited elimination. Since PROCYSBI has a different formulation and posology compared to Cystagon (delayed release vs. immediate release), efficacy data is needed in order to allow the comparability of PROCYSBI's treatment effect to the one of the reference product.

2.5. Clinical efficacy

2.5.1. Dose response study

- **Protocol Number**: RP103-01

Study title: A Pilot Study to Assess the Safety, Tolerability and Pharmacokinetics and Pharmacodynamics of Cysteamine Bitartrate Delayed-release Capsules (RP103), Compared to Cysteamine Bitartrate Capsules, (Cystagon) in Patients with Nephropathic Cystinosis

Protocol summary and results

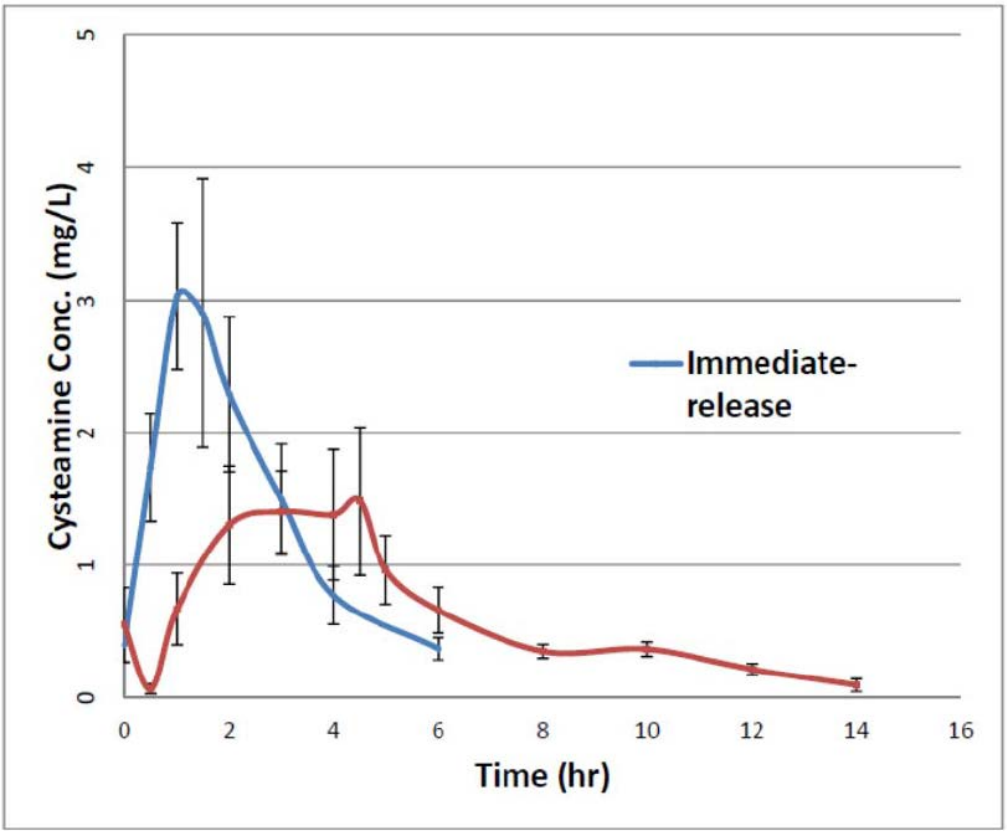
The purpose of Study RP10-01 was to plan for the design of the confirmatory pharmacokinetic and pivotal pharmacodynamic study i.e., Study RP103-03 and to evaluate the safety and tolerability of RP103.

Study RP103-01 was a single center, single dose, open-label, nonrandomized 2-period study. The objective of the study was to assess the PK (i.e., C_{max}, T_{max} and AUC), PD (i.e., WBC cystine levels), and potential safety and tolerability of RP103 compared with Cystagon in subjects with nephropathic cystinosis.

Up to ten (10) subjects were planned, nine (9) subjects were enrolled, and nine (9) subjects completed the study. No patients were terminated from the study or discontinued the study. The study was conducted under fasting conditions and all patients were well-controlled on Cystagon at baseline.

This study demonstrated that there is a highly variable inter-patient bioavailability with the studied formulations, which is attributed to, in part, specific gastric/intestinal motility in children with cystinosis. The study demonstrated that pharmacokinetics of RP103 was consistent with a delayed-release formulation showing a later Tmax (2.78 ± 1.56 and 1.22 ± 0.51 h for RP103 and Cystagon, respectively) but also a longer terminal half-life (5.85 ± 2.89 and 1.90 ± 0.58 h for RP103 and Cystagon, respectively), due to a rate of absorption slower than the rate of elimination, potentially allowing a Q12H dosing instead of Q6H for Cystagon.

Figure 1. RP103-01: Mean plasma concentration of cysteamine in patients receiving 450 mg oral single doses of Cystagon and RP103



There were no obvious difference between the cysteamine plasma concentration versus WBC cystine response between RP103 and Cystagon.

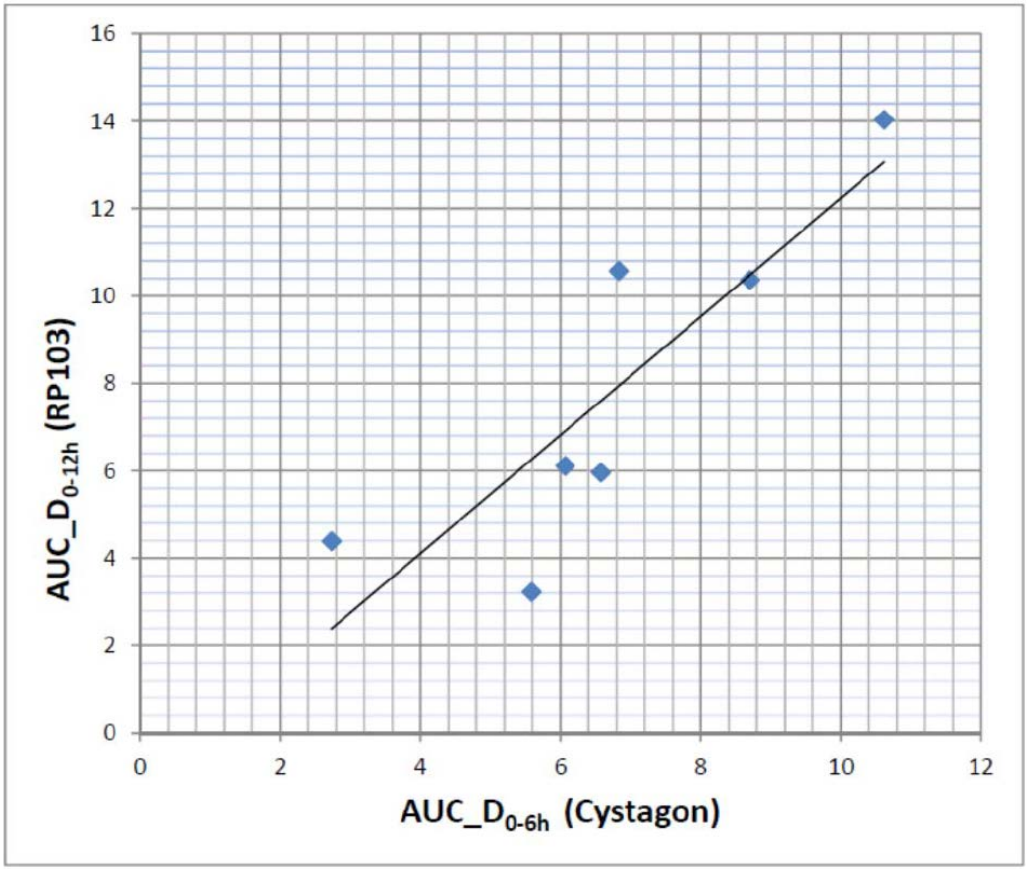
The results suggest that cysteamine concentrations exceeding 10-15 µmol/L are not likely to provide any further effect on the WBC cystine response.

A regression analysis was performed for Cystagon and RP103, see Figure 2.

Regression analysis (Figure 2) of dose-normalized AUC_$D_{0\text{-}12h}$ for RP103 versus dose-normalized AUC_$D_{0\text{-}6h}$ for Cystagon, indicated that the total exposure over 12 hours from RP103 was approximately 140% greater than that over 6 hours for the immediate-release formulation despite using half the daily dose for RP103 compared to immediate-release cysteamine bitartrate capsules. 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 have to be equal to 140% of a single dose of an immediate-release cysteamine bitartrate formulation, which corresponds to a daily dose of RP103 equal to 70% of a daily dose of immediate-release cysteamine bitartrate capsules.

It is considered that the poor correlation between dose and AUC is due to a high inter-patient variability in absorption and elimination of cysteamine despite a low intra-patient variability.

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)



The choice of a PROCYSBI dose which corresponds to a daily dose equal to 70% of Cystagon daily dose, in patients with cystinosis, is supported by previous findings suggesting that direct delivery to the small intestine leads to higher absorption of cysteamine comparatively to delivery to the stomach. This lower daily dose of RP103 should result in plasma concentrations of cysteamine at Q12H after dosing able to maintain therapeutic WBC cystine levels, potentially with fewer side-effects.

2.5.2. Main study

- **Protocol Number:** RP103-03

Study Title: A Randomized Crossover, Pharmacokinetic and Pharmacodynamic Study to Determine the Safety and Efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103), Compared to Cystagon in Subjects with Nephropathic Cystinosis

Methods

Study Participants

Pediatric or adult male or female subjects with nephropathic cystinosis who were on a stable dose of Cystagon sufficient to maintain their white blood cell (WBC) cystine level at ≤2.0 nmol ½ cystine/mg protein were enrolled into the study.

- Inclusion Criteria

Subjects were considered eligible for study enrolment if they satisfied each of the following inclusion criteria:

1. Male or female subjects with a documented diagnosis of nephropathic cystinosis.

2. Subject must be on a stable dose of Cystagon considered by the Investigator as sufficient to maintain their WBC cystine level at ≤2.0 nmol ½ cystine/mg protein.

3. Subject must be able to swallow their typically administered Cystagon capsule with the capsule intact.

4. 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 BSA) at Screening as determined by the Investigator.

5. Subject must have an estimated GFR (corrected for BSA) >30 mL/minute/1.73m2.

6. 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. Subjects must be willing and able to comply with the study restrictions and requirements.

8. Subjects or their parent or guardian must provide written informed consent and assent (where applicable) prior to participation in the study.

- Exclusion Criteria

A prospective subject was excluded from the study if:

1. Subject's age <6 years old or subjects weight <21 kg.

2. Subjects with current history of the following conditions or any other health issues that made 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.

3. Subject had 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.

4. Subjects received any form of cysteamine medication through a gastric tube.

5. Subjects who were receiving maintenance dialysis or who have had a kidney transplant.

6. Subjects who were on an active kidney transplant list or who were planning to receive a kidney transplant within 3 months of Screening.

7. Subjects with known hypersensitivity to cysteamine and penicillamine.

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

9. Subjects who had made a blood donation within 30 days of Screening.

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

Treatments

RP103 in 25 mg and 75 mg capsule formulations and Cystagon in 50 mg and 150 mg capsule formulations are oral formulations of delayed-release and immediate-release cysteamine bitartrate, respectively, whose dosage is expressed as mg of cysteamine free base.

Subjects entering this study must have been on a stable dose of Cystagon considered by the Investigator as sufficient to maintain their WBC cystine level at ≤2.0 nmol ½ cystine/mg protein. Based on previous studies (e.g., RP103-01), a dose of RP103 up to 167% of the total daily Cystagon dose was found to be safe and well-tolerated. Initially, the starting daily dose of RP103 for Periods 1 and 2 was 70% of the end total daily dose of Cystagon during the Run-in Period, with a potential increase of 25% of the actual dose of RP103, which corresponded to approximately 92% of the previous Cystagon dose. Subsequently, following Amendment 4, the starting dose regimen for newly enrolled subjects receiving RP103 was 80% of their end of Run-in Period total daily Cystagon dose. A RP103 dose increase to 100% of their end of Run-in Period Cystagon total daily dose was allowed after review of safety and the results of the WBC cystine levels obtained from blood samples collected during the first week of RP103 treatment in either Period 1 or Period 2.

Subjects were treated with RP103 or Cystagon at their assigned dose level. RP103 was administered every 12 hours and Cystagon was administered every 6 hours.

Objectives

The primary objective of the study was to demonstrate that at steady-state, subjects receiving every 12 hour treatment regimen of RP103 can maintain a comparable depletion of WBC cystine levels after receiving every 6 hour treatment of Cystagon.

The secondary objectives of the study were to:

- Assess the safety and tolerability of RP103
- Assess the steady-state PK and PD of RP103 compared to Cystagon.

Outcomes/endpoints

The primary efficacy measurement was WBC cystine levels at specific time points during administration of RP103 and Cystagon in a cross-over design.

Exploratory end-points were PedsQL or SF-26 scores, use of concomitant gastric acid reduction therapies, and Visual Analog Scale (VAS) for swallowing difficulty.

Sample size

A minimum of 30 subjects was initially calculated to be randomized for this study. Sample size re-estimation based on the intra-subject variance of WBC cystine levels was planned to take place once 20 evaluable subjects completed the study.

The initial sample size re-estimation was done on 17 January 2011. At that time, 36 subjects had been randomized and 34 subjects, of which 22 had complete data, were used for the re-estimation analysis. The initial sample size re-estimation indicated that a total of 30 subjects were needed. However, a calculation error in the reporting of WBC cystine levels was identified and the sample size re-estimation was re-done on 11 February 2011. The reanalysis indicated that a total sample size of 36 subjects was required.

Randomisation

At the end of the Run-in Period and prior to the start of Period 1, subjects were randomized to one of two treatment sequences; 3 weeks (±3 days) treatment with Cystagon every 6 hours followed by crossover to 3 weeks (±3 days) of RP103 every 12 hours or the reverse sequence (RP103 followed by crossover to Cystagon). Qualifying subjects were stratified based on their level of WBC cystine determined the Run-in Period (Group L: ≤1.0 nmol ½ cystine/mg protein; Group H: >1.0 ≤2.0 nmol ½ cystine/mg protein) then randomized to one of the two treatment sequences.

Blinding (masking)

This was an open label study. The Applicant has explored various scenarios for administering the study medication in a blinded manner. However due to the following reasons:

- dose is variable and is determined not by body weight but by their final level of WBC cysteine

and

- the use of placebo in order to mask the difference in posology for the two treatments was not found appropriate since cysteamine capsules have a specific smell and moreover, cyteamine intake is associated with post-dosing bad breath,

it has been concluded that blinding is not feasible to be implemented in this study.

- Identity of Investigational Products

PROCYSBI: RP103 is a beaded, enteric-coated, delayed-release form of the bitartrate salt of cysteamine (an aminothiol, β-mercaptoethylamine), whose microsphere beads are hard-gelatin encapsulated and intended for oral administration. RP103 was available for use in this study in 25 mg and 75 mg capsules (expressed as cysteamine free-base).

Cystagon: Cystagon (immediate-release cysteamine bitartrate) capsules are hard gelatin capsules, available as either 50 mg or 150 mg cysteamine free base, are white, opaque capsules printed with Mylan on the cap and either CYSTAGON 150 or CYSTA 50 on the capsule body. The 150 mg capsules are size 0 and were provided in 500-count bottles; 50 mg capsules are smaller, size 3, and were provided in 500-count bottles.

Statistical methods

The following subject populations were evaluated and used for presentation and analysis of the data.

The Per Protocol efficacy analysis set includes all subjects in the full efficacy analysis set excluding those who meeting any of the conditions below that correspond to measurements under Cystagon:

1) Average WBC cystine levels >2 nmol ½ cystine/mg protein during the Run-in (Day 3, 4, 5)

2) Average WBC cystine levels >2 nmol ½ cystine/mg protein during Period 1 (Week 4) (for subjects receiving Cystagon during Period 1)

3) Average WBC cystine levels >2 nmol ½ cystine/mg protein during Period 1 (Week 6, 0 hours) (for subjects receiving Cystagon during Period 1)

4) Average WBC cystine levels >2 nmol ½ cystine/mg protein during Period 2 (Week 7) (for subjects receiving Cystagon during Period 2)

5) Average WBC cystine levels >2 nmol ½ cystine/mg protein during Period 2 (Week 9, 0 hours) (for subjects receiving Cystagon during Period 2)

The Per Protocol efficacy analysis set is primary.

The safety analysis set includes all subjects who received at least one dose of study drug (RP103 or Cystagon).

Subjects who did not receive their full-intended dose of study drug may have been replaced at the discretion of the Sponsor.

Formal statistical hypothesis testing will be performed on the primary efficacy endpoint only. The primary hypothesis will be addressed by testing the fixed effect of Treatment. If the one-

sided test of non-inferiority, conducted at the nominal level of 0.02104 is rejected at a non-inferiority margin of 0.3, it will be conclude that RP103 is non-inferior to Cystagon with an overall significance level of 0.025.

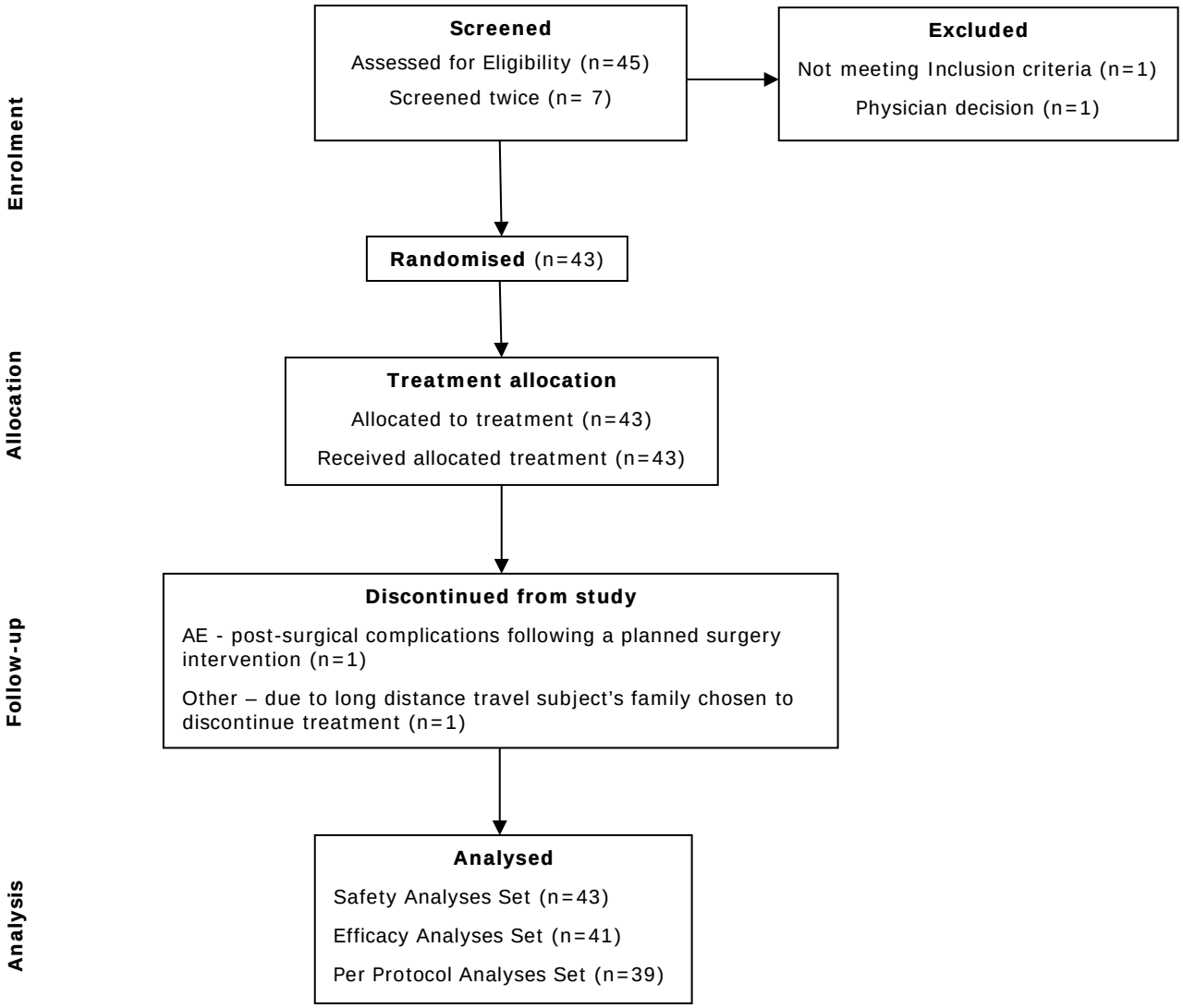
Summary tabulations are presented for appropriate demographic, baseline, efficacy, PK/PD and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter are presented. For continuous variables, N, the mean, median, standard deviation (SD), minimum and maximum values are presented.

All output was incorporated into Microsoft Word files, sorted and labeled according to the ICH recommendations, and formatted to the appropriate page size(s).

All descriptive statistical analyses were performed using SAS statistical software (Version 9.1.3 or later), unless otherwise noted. Medical History and AEs were coded using MedDRA version 13.0. Concomitant medications were coded using the World Health Organization-Drug Reference List (WHO-DRL) version June 2010.

Results

Participant flow



Recruitment

Of 45 subjects who were initially screened, 7 subjects were screened twice (Subjects 01004, 02104, 02105, 02106, 02107, 02109, and 03101) with at least 3 weeks of stable dose of Cystagon before the second screening. Overall, only one subject was a screening failure (Subject 02105) allowing for 44 subjects to be enrolled of which one additional subject (Subject 05001) was discontinued before randomization (physician's decision) resulting in 43 subjects who were randomized to one of two treatment sequences; 3 weeks (±3 days) treatment with Cystagon every 6 hours followed by crossover to 3 weeks (±3 days) of RP103 every 12 hours or the reverse sequence (RP103 followed by crossover to Cystagon).

Conduct of the study

- Protocol amendments

The first version of the RP103-03 protocol that was submitted to FDA was dated 21 November 2009 (Version 1.1). Subsequently, Protocol Amendment 1 was dated 21 February 2010;

Protocol Amendment 2 was dated 03 May 2010; Protocol Amendment 3 was dated 22 July 2010; and Protocol Amendment 4 was dated22 October 2010. These amendments were generated to progressively incorporate FDA input from a special protocol assessment (SPA) process the FDA recommended Raptor follow at the End-of-Phase 2 meeting.

The rationale for Amendment 1 (21 February 2010) was to revise aspects of the protocol design to update and clarify study endpoints and analysis plans, update and finalize sample size estimate, and add collection of PK data to the study design. In addition, the study schedule and procedures were changed to reduce discomfort and impact to the subject and their family. Minor editorial changes were made to clarify statements and instructions and correct typographical and formatting errors in the protocol. However, no-one was enrolled under Amendment 1 as no site was permitted to enrol until Amendment 2 was agreed upon with the FDA and sites had Institutional Review Board (IRB) or Ethics Committee (EC) approval of Amendment 2.

Amendment 2 (03 May 2010) was intended to incorporate input from the FDA. The most significant revisions included the addition of a Run-in Period and randomized parallel crossover which allowed for Cystagon dose adjustment. Inclusion and exclusion criteria were modified to establish entry criteria for subjects with low WBC cysteine levels, specify subject age and weight restrictions, and provide specific parameters for clinically significant changes in liver and renal function. Study objectives, endpoints, and analysis plans were updated. Minor editorial changes were made to clarify statements and instructions and correct typographical and formatting errors in the protocol.

Amendment 3 (22 July 2010) was intended to incorporate input from the FDA. The most significant revisions included restricting study participation to those subjects with a 3-day average WBC cystine level ≤2 nmol ½ cystine/mg protein during Week 2 of the Run-in Period; adjustment of RP103 PD sampling timepoints to ensure appropriate collection; including stratification of subjects according to baseline WBC cystine levels; eliminating one week from

the Run-in Period; and setting the minimum sample size to 30 subjects. Inclusion criteria were modified to include subjects with WBC cystine levels ≤2 nmol/1/2 cystine/mg protein. Minor editorial changes were made to clarify statements and instructions and correct typographical and formatting errors in the protocol.

Amendment 4 (22 October 2010) was intended primarily to change the starting total daily dose of RP103 from 70% to 80% at the end of the Run-in Period Cystagon total daily dose and allow a maximum RP103 dose increase to 100% at the end of the Run-in Period Cystagon total daily dose, with additional information on the background and rationale for the change in RP103 starting dose. Minor editorial changes were made to clarify statements and instructions and correct typographical and formatting errors in the protocol.

- Correction of efficacy results

A calculation error was discovered at the bioanalytical lab that resulted in a 25% decrease in all reported subject white blood cell (WBC) cysteine concentrations from clinical studies Study RP103-03 and Study RP103-04. Because the error was in the calculation of the standard calibrators, it resulted in an overstatement of all cystine results, from both the RP103 and Cystagon arms. The error affected all samples equally and therefore the correction does not alter the conclusion of non-inferiority in Study RP103-03.

Baseline data

Of the 43 subjects included in the Safety population, 27 (62.8%) were children who were in the age range of >2 and ≤12 years. Of these, 16 were male and 11 were female. In the adolescent age range of >12 and ≤21 years age range, which included 15 (34.9%) subjects, 8 subjects were male and 7 were female. In the adult age range of >21 years, there was only 1 subject; a female subject who was 26 years old.

Numbers analysed

43 subjects were randomized and included in the Safety population. Of 41 subjects who completed the study, 39 (95.1%) were included in the Per Protocol data set, 2 subjects not being fully dosing compliant as evidenced by WBC cystine levels that were greater than 2.0 nmol ½ cystine/mg protein, the maximum level allowed per the protocol for study participation at the time of screening.

Outcomes and estimation

- Primary efficacy end point

The results of the analysis of the primary efficacy endpoint of the study, which was a non-inferiority comparison of RP103 to Cystagon in terms of WBC cystine levels, are provided in the below table.

Table 12. Results of PD Parameter of WBC Cystine (nmol ½ Cystine/mg protein) (PP Population / ITT population)

Per –Protocol (PP) Population (N=39)		
	Immediate-release cysteamine bitartrate	PROCYSBI
WBC cystine level (LS Mean ± SE) in nmol hemicystine/mg protein	0.44 ± 0.05	0.51 ± 0.05
Treatment effect (LS mean ± SE; 95.8% CI; p-value)	0.08 ± 0.03 ; 0.01 to 0.15; <0.0001	
All Evaluable Patients (ITT) Population (N=41)		
	Immediate-release cysteamine bitartrate	PROCYSBI
WBC cystine level (LS Mean ± SE) in nmol hemicystine/mg protein	0.74 ± 0.14	0.53 ± 0.14
Treatment effect (LS mean ± SE; 95.8% CI; p-value)	-0.21 ± 0.14 ; -0.48 to 0.06; <0.001	

The mean peak WBC cystine level measured in subjects treated with Cystagon was 0.4367 ±0.05555 nmol ½ cystine/mg protein, compared to an average peak value of 0.5152 ±0.05555 nmol ½ cystine/mg protein for subjects treated with RP103. The mean difference was 0.0785 nmol ½ cystine/mg protein, with a 95.8% CI of 0.0107 to 0.1464.

As stipulated in the SAP, the non-inferiority endpoint of the clinical trial would be achieved if the upper limit of the 95.8% CI of the difference between RP103 and Cystagon was less than the a-priori 0.3 non-inferiority margin, which would correspond to an observed p-value less than or equal to 0.02104 as stipulated in the SAP. The observed p-value was less than 0.0001, thus achieving the non-inferiority endpoint.

- Exploratory end-points

PedsQL 4.0 Generic Core Score

For the PedsQL data, the number of subjects in each age group during Treatment Periods 1 and 2 included 10 or less subjects and at many time points, 5 or fewer subjects were evaluated. Because of the small number of subjects evaluated at each timepoint, it is questionable whether or not the measures that were evaluated had an adequate level of sensitivity for detecting differences over time or between treatments. In general, the median scores suggest that many subjects had reasonably good functionality throughout the study period. However, minimum and maximum scores reveal that at some timepoints, some subjects in both treatment groups were doing very poorly while other subjects were functionally unimpaired.

Visual Analog Scale for Swallowing

Many of the subjects had VAS scores of zero at all time points during both crossover treatment periods. Only 3 subjects had a VAS score greater than 4.0 at a Period 1 or Period 2 time point and all such occurrences were single time point observations. Of these, 1 subject had a score of 10.0 (Subject 02003; Period 2, Week 9, Day 7) while receiving treatment with RP103, 1 subject had a score of 8.0 (Subject 02001; Period 2, Week 9, Day 4) while receiving treatment with Cystagon, and 1 subject had a score of 6.0 (07002; Period 2, Week 9, Day 4) while receiving treatment with RP103. These findings suggest that prior treatment with Cystagon and continued treatment during the Run-In Period with Cystagon had achieved good control of swallowing difficulty due to pain, which continued to be controlled during the crossover Cystagon and RP103 treatment periods.

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13. Summary of Efficacy for trial RP103-03

Title: A Randomized Crossover, Pharmacokinetic and Pharmacodynamic Study to Determine the Safety and Efficacy of Cysteamine Bitartrate Delayed-release Capsules (RP103), Compared to Cystagon in Subjects with Nephropathic Cystinosis			
Study identifier	RP103-03		
Design	This was a non-inferiority phase III study. It was designed as an open-label, randomized crossover outpatient study of the safety, efficacy, tolerability, PK and PD of RP103 in paediatric and adult subjects with nephropathic cystinosis.		
	Duration of main phase:		6 weeks
	Duration of Run-in phase:		2 to 3 weeks
	Duration of Extension phase:		not applicable
Hypothesis	Non-inferiority: To demonstrate that at steady-state, subjects receiving an every 12 hour treatment regimen of RP103 can maintain a comparable depletion of WBC cystine levels after receiving every 6 hour treatment of Cystagon		
Treatments groups	PROCYSBI		3 weeks (±3 days) treatment with PROCYSBI every 12 hours followed by crossover to 3 weeks (±3 days) of Cystagon every 6 hours.
	Cystagon		3 weeks (±3 days) treatment with Cystagon every 6 hours followed by crossover to 3 weeks (±3 days) of RP103 every 12 hours. 43 subjects randomized overall
Endpoints and definitions	Primary endpoint	WBC Cystine	WBC cystine levels at specific time points during administration of RP103 and Cystagon in a cross-over design

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol - full efficacy analysis set excluding those who do not attain WBC cystine levels >2 nmol ½ cystine/mg protein during Cystagon treatment study periods		
Descriptive statistics and estimate variability	Treatment group	Cystagon	PROCYSBI
	Number of subjects	39	
	WBC Cystine (LS Mean)	0.44	0.51
	(SE)	± 0.05	± 0.05
Effect estimate per comparison	WBC Cystine	Comparison groups	PROCYSBI vs. Cystagon
		Treatment effect (LS mean ± SE)	0.08 ± 0.03
		CI 95.8%	0.01 to 0.15
		P-value	<0.0001
Notes	A calculation error was discovered at the bioanalytical lab that resulted in a 25% decrease in all reported subject white blood cell (WBC) cysteine concentrations from clinical studies Study RP103-03 and Study RP103-04. The error affected all samples equally and is the above results are the corrected ones		

Supportive study

- **Study Protocol**: RP103-04

Study Title: A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-release Capsules (RP103) in Patients with Nephropathic Cystinosis

This is a long-term, open-label study of the safety, efficacy, tolerability and steady-state pharmacokinetics and pharmacodynamics of RP103 in pediatric and adult patients with nephropathic cystinosis.

The primary objective of this study is to assess the safety and tolerability of long-term repeat dosing of RP103 in patients with nephropathic cystinosis.

Enrolment in Study RP103-04 was offered to all patients who completed the RP103-03 efficacy study. Forty of forty-one patients who completed the pivotal RP103-03 study chose to enrol in this RP103-04 study. The first patients to enrol in Study RP103-04 have been treated with RP103, with potential dose adjustment by the Investigators based on at least six (6) monthly WBC cystine results (then tested quarterly), since August 2010. Investigators have access to WBC cystine levels for their patients participating in the study. As of 22 Jun 2012 there are 38 patients from RP103-03 continuing in this study. The study has thus far demonstrated that cystinosis patients on a treatment regimen of Q12H dosing with RP103 have been able to maintain a WBC level < 1 nmol ½ cystine/mg protein over at least one year, and at a significantly lower daily dose compared to Cystagon.

Subsequent to determination of the non-inferior efficacious and safe dose of RP103 versus Cystagon and demonstration of the bioequivalence between RP103 administered as either a whole capsule or sprinkled on food or in a liquid, RP103-04 study enrolment was opened to additional subpopulations (i.e. less than 6 years old and post-transplant patients). Although at the time of data cut-off for this submission only limited post screening data were available for these newly enrolled subjects, initial control of their WBC cystine levels after 2 days of treatment during Week 1 on RP103 was attained. Data for these subpopulations will be presented in post marketing.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study RP103-03 is the pivotal study for this application. It was aimed to demonstrate that at steady-state, subjects receiving every 12 hour treatment regimen of RP103 can maintain a comparable depletion of WBC cystine levels after receiving every 6 hour treatment of Cystagon. The cross over design is considered the proper one in order to allow a meaningful comparison between the treatment effects of the two different formulations.

The open-labelled design of the study is considered acceptable since the primary efficacy endpoint is objective and was measured at an independent laboratory with no knowledge of the patients' actual medication. Moreover, according to the applicant's justification, it was not possible to blind the study medication in an appropriate manner. This is agreed by the CHMP.

The non-inferiority margin was set at 0.3 which is considered clinically acceptable since a difference of this magnitude is significantly smaller than the expected effect of Cystagon treatment that decreases the cystine values from >2 to less than 1 nmol ½ cystine/mg/protein .

The inclusion/exclusion criteria are considered reasonable taking into account the characteristics of the disease. Of the 43 subjects recruited in the study and included in the Safety population, 27 (62.8%) were children (age range of >2 and ≤12 years), 15 (34.9%) were adolescents (age range of >12 and ≤21 years) and 1 adult. The recruited population is considered representative for the overall population affected by nephropathic cystinosis.

The major reasons for discontinuations were AEs, in particular gastrointestinal related.

Efficacy data and additional analyses

The relative bioavailability of RP103 compared to immediate release cysteamine (Cystagon), based on PK data, in studies RP103-01 and RP103-03 is 109-129% and approximately 125% respectively. This is appropriately reflected in the SmPC.

Treatment with RP103 given twice daily has been demonstrated to be non-inferior to that of Cystagon administered four times daily. Due to low number of patients and short length of the evaluation period the data related to the secondary endpoints doesn't allow drawing conclusion that would be supportive. Where quality of life has been formally measured the number of respondents is low and there are sometimes apparently large changes between treatments and time-points making the data difficult to interpret. Improvements in quality of

life have been seen among those patients who enrolled in study RP103-04, and have remained on RP103 treatment on a long-term basis.

The Applicant has presented long term efficacy data that suggest that treatment with RP103 every 12 hours for up to one year, in the majority of patients, maintains the WBC level < 1 nmol ½ cystine/mg protein.

However, the effect of cysteamine in the treatment of cystinosis is well-established and RP103 has been shown to be at least as effective as Cystagon in maintaining the cystine at acceptable levels. The dosing schedule for RP103 twice daily is an advantage, in particular, in the youngest age-group. The impact on compliance with the treatment is expected to be increased.

In the pivotal study, patients receiving RP103 were asked to stop using PPIs. A number of these patients had gastrointestinal side effects during the treatment and could be expected to use PPIs to reduce their symptoms. The Applicant has presented data (study RP103-HLTA-009) that show that the concomitant use of medication increasing the gastric pH (antacids) does not influence the delayed release characteristics of RP103 (please see the pharmacology section for study results). Further, as an extra efficacy measure for patients using antacids, it is recommended that the WBC cystine levels should be checked at regular intervals.

Data from the on-going open labelled safety extension study (RP103-04), where patients from the pivotal study have been followed for up to 15 months, support that the WBC cystine levels are maintained with long-term treatment at the levels aimed for.

The Applicant claimed that apart from the reduced dosing interval there are a number of advantages of RP103 as compared with Cystagon. It was stated that the treatment would constitute a major improvement in compliance and quality of life and also improve the palatability, potential reduce in the frequency of halitosis, improve sleeping patterns and improvement of social participation. Treatment with the new formulation of cysteamine seems to reduce, but not completely eliminate, these disadvantages.

2.5.4. Conclusions on the clinical efficacy

The clinical efficacy of RP103 has been shown to be similar to that of Cystagon with a dosing schedule that may promote a better compliance. The Applicant has presented data showing that the concomitant use of medication increasing the gastric pH (antacids) do not influence the delayed release characteristics of RP103.

2.6. Clinical safety

Patient exposure

The first study (RP103-01) conducted with RP103 was a pilot study to provide information for the design of the planned phase III study. This examined the pharmacokinetics (PK) and pharmacodynamics (PD) of cysteamine in 9 patients initially treated with Cystagon followed the next day by a single dose of RP103. Treatment with Cystagon continued 12 hours after the dose of RP103.

The phase III study (RP103-03) was a randomised crossover study conducted in 43 patients treated with RP103 q12h delayed-release capsule followed by Cystagon q6h or vice versa. Each treatment was for 3 weeks ± 3 days.

Patients completing study RP103-03 were eligible to enter a Long-Term, Open-Label, Safety and Efficacy Study (RP103-04). Additional patients, who did not complete the RP103-03 study, were permitted to be enrolled when results of study RP103-03 demonstrated non-inferiority of RP103 versus Cystagon in reducing WBC cystine levels. So far, 37 patients have been treated for ≥ 10 months and 27 for 15 months (data cut-off 22 Jun 2012) in this study.

In addition, three studies (RP103-02, RP103-05 and RP103-06) were conducted in healthy volunteers to demonstrate bioequivalence (BE). In each of the three studies, the rate and extent of absorption of two different modes of RP103 were compared. Two modes of administration (intact delayed release capsule, and content of open delayed released capsule mixed in pudding small amount of food) were compared with each subject receiving the two doses in random sequence. The results of the first study (RP103-02) in fed healthy volunteers were non-interpretable due to the discovery of a food effect. The subsequent BE studies (RP103-05 and RP103-06), in fasted healthy volunteers, demonstrates RP103 capsules taken as whole capsules are bioequivalent to RP103 capsules sprinkled on a small amount of food. There were 18 subjects in study RP103-02, 20 in RP103-05, and 20 in RP103-06.

Adverse events

Summaries of adverse events in healthy volunteers and in cystinosis patients are presented in the tables below.

Table 14. Healthy volunteer treatment-emergent adverse events (Safety population)

	RP103-02			RP103-05			RP103-06		Total
MedDRA SOC/ Preferred Term	**Stage I Open (N=17) n (%)**	**Stage I Intact (N=18) n (%)**	**Stage III Fasted Intact (N=4) n (%)**	**Stage I Open (N=20) n (%)**	**Stage I Intact (N=19) n (%)**	**Parallel Group Meal Delay Period 3 (N=17) n (%)**	**Open (N=20) n (%)**	**Intact (N=19) n (%)**	**Total (N=58) n (%)**
No. of Subjects with Any AE	4 (23.5)	5 (27.8)	2 (50.0)	7 (35.0)	5 (26.3)	10 (58.8)	3 (15.0)	7 (36.8)	35 (60.3)

Gastrointestinal disorders	1 (5.9)	1 (5.6)	1 (25.0)	5 (25.0)	3 (15.8)	9 (52.9)	2 (10.0)	5 (26.3)	23 (39.7)
Diarrhoea	0 (0.0)	1 (5.6)	1 (25.0)	1 (5.0)	0 (0.0)	7 (41.2)	2 (10.0)	3 (15.8)	14 (24.1)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)	7 (41.2)	1 (5.0)	3 (15.8)	14 (24.1)
Abdominal pain	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	2 (11.8)	1 (5.0)	2 (10.5)	6 (10.3)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	3 (17.6)	0 (0.0)	1 (5.3)	6 (10.3)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (23.5)	0 (0.0)	0 (0.0)	4 (6.9)
Abdominal discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Abdominal pain lower	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Breath odour	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	1 (1.7)
Eructation	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Nervous systems disorders	2 (11.8)	2 (11.1)	0 (0.0)	1 (5.0)	1 (5.3)	3 (17.6)	1 (5.0)	2 (10.5)	11 (19.0)
Headache	1 (5.9)	1 (5.6)	0 (0.0)	0 (0.0)	1 (5.3)	3 (17.6)	0 (0.0)	1 (5.3)	7 (12.1)
Dizziness	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	3 (5.2)
Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	1 (1.7)
Somnolence	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (17.6)	0 (0.0)	2 (10.5)	5 (8.6)
Pallor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (17.6)	0 (0.0)	2 (10.5)	5 (8.6)
Musculoskeletal and connective tissue disorders	1 (5.9)	1 (5.6)	1 (25.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.9)
Back pain	0 (0.0)	1 (5.6)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)
Neck pain	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)
Pain in jaw	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.0)	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.9)
Urine odour abnormal	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.2)
Haematuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Pollakiuria	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	2 (10.5)	4 (6.9)
Cold sweat	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.59)	0 (0.0)	2 (10.5)	3 (5.2)
Acne	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.59)	0 (0.0)	0 (0.0)	1 (1.7)
Immune system disorders	0 (0.0)	0 (0.0)	1 (25.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)
Anaphylactic reaction	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Infections and infestations	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	2 (3.4)
Gastroenteritis	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.7)

Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	2 (3.4)
Vision blurred	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	2 (3.4)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.7)
Ear pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.7)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.53)	1 (1.7)
Vision blurred	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.53)	1 (1.7)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.53)	1 (1.7)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.53)	1 (1.7)

Notes: RP103-02 Stage I patients consisted of those receiving sequence Open/Intact + Intact/Open. Four (4) subjects who completed RP103-02 Stage I returned to the clinic for Stage III and received a single 600 mg dose of RP103 intact capsules in the fasted state. RP103-05 Stage I consisted of Periods 1 and 2 in a Bioequivalence design. Period 3 consisted of a parallel-group design with four (4) treatment meal delay schedules.

Table 15. Cystinosis patients treatment-emergent adverse events (Safety population)

MedDRA SOC/ Preferred Term	RP103-01		RP103-03		Overall[1]		Fisher's Exact P-value
	Cystagon® (N=9) n (%)	RP103 (N=9) n (%)	Cystagon® (N=41) n (%)	RP103 (N=43) n (%)	Cystagon® (N=50) n (%)	RP103 (N=52) n (%)	
No. of Subjects with Any TEAE	8 (88.9)	2 (22.2)	13 (31.7)	25 (58.1)	21 (42.0)	27 (51.9)	0.3296
Gastrointestinal disorders	7 (77.8)	0 (0.0)	9 (22.0)	14 (32.6)	16 (32.0)	14 (26.9)	0.6654
Nausea	4 (44.4)	0 (0.0)	5 (12.2)	8 (18.6)	9 (18.0)	8 (15.4)	0.7941
Vomiting	3 (33.3)	0 (0.0)	3 (7.3)	7 (16.3)	6 (12.0)	7 (13.5)	1.0000
Abd. pain	1 (11.1)	0 (0.0)	0 (0.0)	4 (9.3)	1 (2.0)	4 (7.7)	0.3629
Diarrhoea	1 (11.1)	0 (0.0)	1 (2.4)	1 (2.3)	2 (4.0)	1 (1.9)	0.6139
Abd. discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Abd. pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Breath odour	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Constipation	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Mouth ulceration	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
General disorders & admin. site conditions	4 (44.4)	2 (22.2)	0 (0.0)	4 (9.3)	4 (8.0)	6 (11.5)	0.7415
Thirst	4 (44.4)	2 (22.2)	0 (0.0)	0 (0.0)	4 (8.0)	2 (3.8)	0.4320
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Med. device site reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Metabolism & nutrition disorders	1 (11.1)	0 (0.0)	3 (7.3)	4 (9.3)	4 (8.0)	4 (7.7)	1.0000
Hypokalaemia	1 (11.1)	0 (0.0)	0 (0.0)	3 (7.0)	1 (2.0)	3 (5.8)	0.6178
Decreased appetite	0 (0.0)	0 (0.0)	2 (4.9)	1 (2.3)	2 (4.0)	1 (1.9)	0.6139
Anorexia	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Hypertriglyceridaemia	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Hypovolaemia	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Nervous system disorders	0 (0.0)	0 (0.0)	1 (2.4)	6 (14.0)	1 (2.0)	6 (11.5)	0.1125
Headache	0 (0.0)	0 (0.0)	0 (0.0)	4 (9.3)	0 (0.0)	4 (7.7)	0.1179
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)	2 (3.8)	0.4952
Somnolence	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.3)	1 (2.0)	1 (1.9)	1.0000
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Vascular disorders	1 (11.1)	0 (0.0)	1 (2.4)	4 (9.3)	2 (4.0)	4 (7.7)	0.6783
Flushing	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.3)	1 (2.0)	1 (1.9)	1.0000
Pallor	1 (11.1)	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.0)	1 (1.9)	1.0000
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Cardiac disorders	0 (0.0)	0 (0.0)	4 (9.8)	1 (2.3)	4 (8.0)	1 (1.9)	0.2004
Atrioventricular block	0 (0.0)	0 (0.0)	2 (4.9)	0 (0.0)	2 (4.0)	0 (0.0)	0.2378
Left ventricular hypertrophy	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Tachycardia	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Ventricular hypertrophy	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Skin & subcutaneous tissue disorders	1 (11.1)	0 (0.0)	1 (2.4)	3 (7.0)	2 (4.0)	3 (5.8)	1.0000
Rash	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.3)	1 (2.0)	1 (1.9)	1.0000
Cold sweat	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Skin odour abn.	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Infections & infestations	0 (0.0)	0 (0.0)	1 (2.4)	3 (7.0)	1 (2.0)	3 (5.8)	0.6178
Nasopharyngitis	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.3)	1 (2.0)	1 (1.9)	1.0000
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Renal & urinary disorders	0 (0.0)	0 (0.0)	1 (2.4)	3 (7.0)	1 (2.0)	3 (5.8)	0.6178
Renal impairment	0 (0.0)	0 (0.0)	1 (2.4)	2 (4.7)	1 (2.0)	2 (3.8)	1.0000
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Injury, poisoning & procedural complications	1 (11.1)	0 (0.0)	0 (0.0)	2 (4.7)	1 (2.0)	2 (3.8)	1.0000
Contusion	1 (11.1)	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.0)	1 (1.9)	1.0000
Femur fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3	0 (0.0)	1 (1.9)	1.0000
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (2.4)	2 (4.7)	1 (2.0)	2 (3.8)	1.0000
Joint stiffness	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Knee deformity	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000

Infections & infestations	0 (0.0)	0 (0.0)	1 (2.4)	3 (7.0)	1 (2.0)	3 (5.8)	0.6178
Nasopharyngitis	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.3)	1 (2.0)	1 (1.9)	1.0000
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Renal & urinary disorders	0 (0.0)	0 (0.0)	1 (2.4)	3 (7.0)	1 (2.0)	3 (5.8)	0.6178
Renal impairment	0 (0.0)	0 (0.0)	1 (2.4)	2 (4.7)	1 (2.0)	2 (3.8)	1.0000
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Injury, poisoning & procedural complications	1 (11.1)	0 (0.0)	0 (0.0)	2 (4.7)	1 (2.0)	2 (3.8)	1.0000
Contusion	1 (11.1)	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.0)	1 (1.9)	1.0000
Femur fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3	0 (0.0)	1 (1.9)	1.0000
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (2.4)	2 (4.7)	1 (2.0)	2 (3.8)	1.0000
Joint stiffness	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Knee deformity	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Respiratory, thoracic & mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.0)	0 (0.0)	3 (5.8)	0.2429
Cough	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)	2 (3.8)	0.4952
Oopharyngeal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Respiratory tract congestion	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Investigations	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.3)	1 (2.0)	1 (1.9)	1.0000
ECG QT prolonged	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Haemoglobin decreased	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.0)	0 (0.0)	0.4902
Ear & Labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Deafness	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.9)	1.0000

MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class; No.=number; TEAE=treatment-emergent adverse event; Abd.=abdominal

[1] Six patients were enrolled in both studies RP103-01 and RP103-03 (subjects RP103-03-01-005, RP103-03-02-107, RP103-03-02-002, RP103-03-03-004, RP103-03-03-002, and RP103-03-02-106). These patients were counted twice accordingly in the Overall columns

Overall, the most common adverse events were gastrointestinal disorders like nausea, vomiting, diarrhoea and abdominal pain, general disorders and administration site conditions, metabolism and nutrition disorders and nervous system disorders.

According to Cystagon's PI approximately 35 % of patients experience side effects at the initiation of therapy, mainly involving the gastrointestinal and central nervous systems. It is recommended to interrupt and gradually and re-start the treatment in order improve tolerance.

A second interim report from Study RP103-04 has been presented by the Applicant (data cut-off 22 Jun 2012). Sixty patients have been enrolled in the study, 40 patients that previously completed Study RP103-03 and 20 that were newly recruited. Overall 85 % (n=51) have experienced one or more TEAEs and 47 % (n=28) had treatment-related TEAEs. The majority of treatment related TEAEs were gastrointestinal disorders (vomiting, abdominal pain, nausea, breath odour and diarrhoea) as well as skin odour abnormal and decreased appetite. The majority of TEAEs were of mild or moderate intensity. There were 19 SAEs reported of which 2 were considered to be possibly related to the study drug (Grade 3 constipation and Grade 2 diarrhoea). For 2 patients the TEAEs were classified as Grade 4 (life-threatening) (unrelated hypocalcaemia and appendicitis).

Serious adverse event / deaths / other significant events

Overall there have been 3 patients with serious adverse events (one in the pivotal study and two in the extension study) that were considered to be related to RP103 (abdominal discomfort, constipation and diarrhoea).

A significant adverse event was reported in one healthy volunteer. The subject had a possible anaphylactic reaction and required hospitalization for treatment of nausea, emesis and significant orthostatic and vital sign changes.

One significant adverse reaction occurred in a patient that that experienced intermittent vomiting Grade 2 on two occasions separated by 3 weeks. After temporal interruption of the treatment, for 3 and 8 days respectively, and a dose reduction from 1900 mg to 1050 mg, the patient was continuing treatment.

Laboratory findings

There were no clinically relevant laboratory, vital sign, or ECG findings that were associated with the treatment with RP103.

Safety in special populations

No studies have been performed in special populations.

Safety related to drug-drug interactions and other interactions

No drug-drug interactions have been described in conjunction with Cystagon and no drug-drug interactions have been identified in the clinical trials conducted with RP103.

Discontinuation due to adverse events

There were 2 patients that discontinued the study drug due to TEAEs in the pivotal study RP103-03. One patient discontinued due to prolonged vomiting (approximately 2 months) that resolved after the discontinuation. The second patient discontinued after experiencing decreased appetite and dyspepsia (both AEs were considered as Grade 1 and probably related).

In the extension study four patients have discontinued, 2 due to TEAEs, 1 per investigator decision and 1 for unspecified (other) reasons. Discontinuations that were treatment-related included intermittent vomiting (one patient) and constant dyspepsia and decreased appetite (one patient)

Post marketing experience

No post-marketing data are available with PROCYSBI. The medicinal product has not been marketed in any country.

Based on the Cystagon's PI benign intracranial hypertension (or pseudomotor cerebri) with papilledema skin lesions, molluscoid pseudotumors, skin striae, skin fragility; joint hyperextension, leg pain, genu valgum, osteopenia, compression fracture and scoliosis have been reported.

Cystagon post marketing reports include one report of interstitial nephritis with early renal failure. A causal relationship between this event and cysteamine bitartrate therapy has not been established.

2.6.1. Discussion on clinical safety

Overall, there were 38 healthy volunteers and 52 patients with cystinosis being exposed to RP103 in the development programme. The majority of healthy subjects received single doses while patients in the pivotal study RP103-03 were administered individual doses twice daily for 3 weeks. In the extension study RP103-04, as of the cut-off date (June 2012), 62 % (n=37) and 45 % (n=27) of the patients have completed ≥ 10 and 15 months of treatment, respectively.

Thus, the safety data base is limited but the active substance is approved in the same indication and has been used in the EU since 1997.

The MedDRA SOC with the highest incidence overall in cystinosis patients were gastrointestinal disorders (27 %) like nausea, vomiting, diarrhoea and abdominal pain, followed by general disorders and administration site conditions (12 %) metabolism and nutrition disorders (8 %) and nervous system disorders (12 %). According to Cystagon's PI approximately 35 % of patients experience side effects at the initiation of therapy, mainly involving the gastrointestinal and central nervous systems. It is recommended to interrupt and gradually re-start the treatment in order improve tolerance.

There are no major safety issues identified in any of the studies and the short-term safety profile of RP103 seems to be similar to that of Cystagon. In the pivotal study the incidence of in particular gastrointestinal adverse events was higher during RP103 treatment than during treatment with Cystagon.

The results from the studies indicate that RP103 is less well tolerated when given in connection with a meal. Intake together with food is also known to reduce the absorption of the drug. This information is properly reflected in section 4.2 of the SmPC.

Data presented from the second interim report from the extension study (RP103-04) include safety data on patients that have been treated for up to 15 months. No unexpected safety findings have been revealed.

In patients administered high doses of cysteamine bitartrate, serious skin lesions have been reported. The skin lesions are described as molluscoid pseudo tumours and were previously classified as Ehlers-Danlos like syndrome that affects collagen structure in skin, joints, and blood vessels.

Serious adverse events reports from patients treated with cysteamine bitartrate involving the gastrointestinal (GI) tract is ulceration. A further GI risk concerns the capsule material used for RP103 that has been regarded as potentially related to fibrosing colonopathy after long-term treatment with pancreatic enzymes in patients with cystic fibrosis. A warning is included in the SmPC section 4.4 in line with already approved products using the same coating. This possible risk is addressed in the RMP as a potential risk.

Other adverse effects that have been connected with the use of cysteamine concern the central nervous system symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy. There are reports that identify cysteamine with reversible leucopoenia and abnormal liver function.

Intracranial hypertension has also been associated with cysteamine bitartrate treatment although a causal relationship to cysteamine has not been established.

There are no studies performed in pregnant and lactating females. Breast-feeding is included as a contraindication in line with the SmPC for Cystagon. The text concerning pregnancy is identical to that of Cystagon. However, the text is not included under contraindication section of the SmPC (as per Cystagon's SmPC) but only under section 4.6 since the text is not worded as strict contraindication but recommends a cautious approach when pregnancy is detected.

From the safety database all the adverse reactions reported in clinical trials and from the post-marketing data with Cystagon have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

There are no major short-term safety issues identified. As it was expected the safety profile of PROCYSBI is similar to that of Cystagon. Further long-term safety data will be made available in December 2013 (3rd interim report from study RP103-04).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan (V 4), the PRAC considers by consensus decision that the risk management system for Mercaptamine bitartrate (PROCYSBI) in the treatment of proven nephropathic cystinosis could be acceptable provided an updated risk management plan and satisfactory responses to the questions detailed in section 4 of the PRAC advice are submitted prior to the CHMP Opinion.

The applicant has submitted an updated version of the Risk Management Plan (V5) which has the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Gastrointestinal (GI) symptoms: vomiting, nausea, diarrhoea, abdominal pain • Encephalopathy

Summary of safety concerns	
Important potential risks	• Teratogenicity • Fibrosing colonopathy • Ehlers-Danlos-like syndrome
Missing information	• Patients with heart disease • Patients with inflammatory bowel disease or resection of the small intestine • Drug-drug interactions • Use in patients on renal replacement therapy and / or renal transplantation • Confirmed somatostatin level reduction and associated hormonal, behavioural or cognitive consequences • Long-term (2+ years) use

Pharmacovigilance plans

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
1) GI symptoms: vomiting, nausea, diarrhoea, abdominal pain	• Warning in section 4.4 of the SmPC cautions regarding the therapy that it may have to be interrupted and the dose adjusted if these symptoms are observed. • Listed under section 4.8 of the SmPC as very common to common undesirable effects *(Very common:* Vomiting, nausea, diarrhoea *Common:* Abdominal pain) • Section 4.2 of the SmPC clearly states that PROCYSBI treatment should be initiated under	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	the supervision of a physician experienced in the treatment of cystinosis.	
2) Encephalopathy	• Warning in section 4.4 of the SmPC that encephalopathy has been associated with cysteamine. If Central Nervous System symptoms develop, the patient should be carefully evaluated and the dose adjusted as necessary. • Listed in section 4.8 as a common undesirable effect. • Section 4.2 of the SmPC clearly states that PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.	• Safety check-list to create awareness of potential risk and long-term exposure to PROCYSBI , complementing PV activities.
3) Teratogenicity	• Warning in section 4.4 of the SmPC that if a pregnancy is diagnosed or planned, the treatment should be carefully reconsidered and the patient must be advised of the possible teratogenic risk of cysteamine. • Recommendation is section 4.6 of the SmPC that PROCYSBI should not be used during pregnancy, particularly during the first trimester, unless clearly necessary. • Section 4.2 of the SmPC clearly states that PROCYSBI treatment	• Safety check-list to create awareness of risk about teratogenicity

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	should be initiated under the supervision of a physician experienced in the treatment of cystinosis.	
4) Fibrosing colonopathy	• Warning in section 4.4. of SmPC that Fibrosing Colonopathy has been reported in patients with cystic fibrosis who were treated with high-dose pancreatic enzymes with an enteric coating of methacrylic acid ethyl acrylate copolymer (Eudragit), one of the excipients of PROCYSBI. • Section 4.2 of the SmPC clearly states that PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.	• Safety check-list complementing the SmPC and PIL to ensure correct selection of patients, proper dosing, setting up arrangements for subsequent monitoring and enhancing awareness of the potential for the possibility of rare and unexpected events will be used.
5) Ehlers-Danlos like syndrome (EDS)	• Section 4.2 of the SmPC clearly states that PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis. • Sections 4.4 and 4.8 of the SmPC contain risk minimisation wording.	• Safety check-list complementing the SmPC and PIL to ensure correct selection of patients, proper dosing, setting up arrangements for subsequent monitoring and enhancing awareness of the potential for the possibility of rare and unexpected events will be used.
Missing Information		
1. Patients with heart disease 2. Patients with inflammatory bowel disease or resection of the small intestine 3. Drug-drug interactions	• Section 4.2 of the SmPC clearly states that PROCYSBI treatment should be initiated under the supervision of a	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
4. Use in patients with renal replacement and / or renal transplantation 5. Confirmed somatostatin level reduction and associated hormonal, behavioural or cognitive consequences 6. Long-term (2+ years) use	physician experienced in the treatment of cystinosis.	

The additional risk minimisation measure proposed, the physician Safety Checklist, is considered by the PRAC as an appropriate reminder and useful tool for strengthening the awareness on identified and potential risks as well as appropriate patient selection, the need for dose titration and patient monitoring. Given that the treatment is a long term one employing it every 6 months is seen as reasonable frequency.

All issues identified by the PRAC were properly addressed by the applicant.

The CHMP endorsed the updated RMP without changes.

PSUR submission

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

Benefits

Beneficial effects

Cysteamine bitartrate (CB) is the only treatment option available for patients with cystinosis. CB has been used in the treatment of cystinosis for over three decades. An immediate release of CB formulation has been available for more than 15 years in the EU (Cystagon). The present hybrid application concerns PROCYSBI (RP103), a delayed-release formulation that should be dosed twice daily as compared with the reference product, Cystagon that should be

administered 4 times daily. The new formulation, due to a less frequent administration schedule, is expected to increase compliance and the quality of life for patients with cystinosis.

Based on the data generated in three bioequivalence studies run in healthy volunteers, PROCYSBI gastro resistant capsule is considered bioequivalent with its content mixed with food or liquid. In addition, coadministration with applesauce or orange juice doesn't affect the PK of cysteamine.

For the youngest children and for patients with difficulties swallowing capsules, the content of the new formulation may be sprinkled on food or liquids which is considered an advantage over the reference product.

Dosing in a fed state (high-fat, high caloric meal 30 minutes before dosing) reduces cysteamine bioavailability therefore PROCYSBI should not be administered with food rich in fat or proteins.

Three clinical studies have been carried out in patients affected by cystinosis, one phase IIb dose finding study (RP103-01), the pivotal phase III study (RP103-03) aimed to demonstrate safe, non-inferiority efficacy of gastro-resistant capsules administered every 12 hours vs. Cystagon and a follow-up long-term open label study (RP103-04) aimed to gather long term information on efficacy and safety of PROCYSBI.

The WBC cystine level is generally accepted as surrogate marker for treatment effect and was included as the primary endpoint in the studies.

The submitted study data supports a consistent delayed-release characteristic of RP103 with a later median tmax (3 hours vs. 1 hour) and a longer half-life (4.23 vs. 1.5 hours) of PROCYSBI as compared to immediate release Cystagon indicating absorption rate limited elimination.

In the pivotal study, non-inferiority of treatment effect was demonstrated for RP103 compared with Cystagon (LS mean±SE; 95.8% CI; p-value: 0.08±0.03; 0.01 – 0.15; < 0.0001). No firm conclusions can be drawn from the data collected for the secondary endpoints due to small number of patients and short term treatment period. However, the effect of cysteamine in the treatment of cystinosis is well-established and Q12h RP103 has been shown to be at least as effective as Q6h Cystagon in maintaining the cystine at acceptable levels.

Data from the on-going open labelled efficacy and safety extension study, where patients from the pivotal study have been followed for up to 15 months, does indicate that the WBC cystine levels are maintained with long-term treatment at the levels aimed for.

Although the body of data is limited, as expected for an orphan indication, there are no major safety issues identified in any of the studies and the safety profile of PROCYSBI seems to be similar to that of Cystagon.

Uncertainty in the knowledge about the beneficial effects

Patients receiving RP103 in the Phase III efficacy study (RP103-03) were asked to refrain from taking any proton pump inhibitors (PPIs) or gastric acid reducing medications 12 hours prior to their first RP103 dose up to study completion. Literature reports indicate that even a single dose of PPI could lead to an increase of stomach pH up to 6 which led to the concern that the gastro-resistant capsules which are designed to dissolve at pH ≥5.5 might not by-pass the

stomach in patients taking PPIs. Therefore the Applicant presented data that show that the concomitant use of medication increasing the gastric pH (antacids) does not influence the delayed release characteristics of RP103 (Study RP103-HLTA-009).

The Applicant claims that apart from the increased dosing interval there are a number of further advantages of PROCYSBI as compared with Cystagon. These were suggested to be improved palatability, potential reduce in the frequency of halitosis, improved sleeping patterns and improvement of social participation. Treatment with the new formulation of cysteamine seems to reduce, but not completely eliminate, these disadvantages. However, compliance with treatment is the most important issue from a clinical point of view that is expected to be increased with the dosing schedule twice daily, in particular, in the youngest age-group.

Throughout the clinical development programme, RP103 and Cystagon have been dosed in both fasted and a number of different fed states (fed 30 min after, fed 2 h after, fed 30 min before, high fat meal, applesauce, chocolate pudding, orange juice).

Data presented by the Applicant indicates in a consistent manner that dosing in a fed state (high-fat, high caloric meal 30 minutes before dosing) reduces cysteamine bioavailability. On the other hand the data indicates that a meal 2 hours after RP103 administration does not affect the PK of cysteamine. Even though the data covers a number of scenarios, the data is based on small studies and no data on meals had 30 minutes to 2 hours before RP103 administration is available. Therefore, the patients should try to consistently avoid meals and dairy products for at least 1 hour before and 1 hour after PROCYSBI dose.

Batches used during the clinical studies contained up to 10% less cysteamine than the proposed label claim due to a calculation error. An increase in amount of active substance is, from an efficacy perspective, acceptable since patients are dosed individually depending on their WBC cystine levels. The mean total daily dose of RP-103 in the pivotal study was 82% of the incoming Cystagon dose and therefore, an increase of amount is not a safety issue.

Risks

Unfavourable effects

The most common short-term safety issues concerns gastrointestinal and central nervous systems side effects. Gastrointestinal and nervous system disorders were also common side effects observed during PROCYSBI's clinical development plan. The safety profile is expected to be similar to that of the reference product.

Serious adverse events reports from patients treated with cysteamine bitartrate involving the gastrointestinal (GI) tract is ulceration.

In patients administered high doses of cysteamine bitartrate, serious skin lesions have been reported. The skin lesions are described as molluscoid pseudo tumours and were previously classified as Ehlers-Danlos like syndrome that affects collagen structure in skin, joints, and blood vessels.

However, the serious hypotensive episode suffered one subject in Study RP103-02 is of concern particularly as it occurs in such a small data base. Therefore, anaphylaxis (the presumed diagnosis) is listed as an AE with unknown frequency in the SmPC section 4.8.

Based on pre-clinical data, teratogenicity is one of the potential safety concerns, therefor a warning in the SmPC regarding pregnancy (see SmPC section 4.4), and a contraindication for breast feeding (see SmPC section 4.3).

Gastrointestinal (GI) symptoms and Encephalopathy are indicated as important identified risks in the RMP; teratogenicity, fibrosing colonopathy and Ehlers-Danlos-like syndrome are listed as important potential risks.

Uncertainty in the knowledge about the unfavourable effects

Long term safety data is limited. Data presented from the second interim report (data from ≥ 10 months for 37 patients and up to 15 months of treatment for 27 patients) from the extension study (RP103-04) did not reveal any unexpected safety findings. Long term data is indicated as missing information in the RMP.

A further potential GI risk concerns the capsule material used for RP103 that has been suspected to be related to fibrosing colonopathy after long-term treatment with pancreatic enzymes in patients with cystic fibrosis. A warning is included in the SmPC section 4.4 in line with already approved products using the same coating and in addition is reflected in the safety checklist (risk minimisation measure).

Intracranial hypertension has also been associated with cysteamine bitartrate treatment although a causal relationship to cysteamine has not been established.

Benefit-risk balance

Importance of favourable and unfavourable effects

Cystinosis is a serious and debilitating disease with a number of complications like the renal Fanconi syndrome. A number of patients suffer from end stage renal failure already by the end of the first decade of life. At present Cystagon (mercaptamine bitartrate) is the only treatment option available for cystinosis patients. To maintain the cystine levels at low levels, Cystagon should be dosed every 6 hours. The clinical efficacy of PROCYSBI has been shown to be similar to the one of the reference product. Twice daily dosing schedule can be considered as an improvement in daily life of these patients and may increase the compliance.

Throughout PROCYSBI clinical development programme, gastrointestinal adverse effects were the most frequently reported, particularly in patients receiving RP103 treatment when asked to stop using PPIs. The Applicant has presented data to show that the concomitant use of medication increasing the gastric pH (antacids) do not influence the delayed release characteristics of PROCYSBI.

No new safety signals have been observed during the studies and it can be considerd that the safety profile of cysteamine is well established. Although the long-term safety data of PROCYSBI are limited, the safety profile is expected to be similar to that of the reference

product. The available Cystagon post-marketing data can be considered reassuring in this respect.

Batches used during the clinical studies contained up to 10% less cysteamine than the proposed label claim due to a calculation error. An increase in amount of active substance is, from an efficacy perspective, acceptable since patients are dosed individually depending on their WBC cystine levels. The mean total daily dose of RP-103 in the pivotal study was 82% of the incoming Cystagon dose and therefore, an increase of amount is not a safety issue.

Benefit-risk balance

This application concerns a hybrid version of mercaptamine hard capsules. The reference product Cystagon is indicated for

“treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.”

This application contains a different pharmaceutical formulation of the active substance. PROCYSBI is a slow release formulation that allows for a twice daily administration schedule and is presented as gelatine capsules filled with enteric coated beads containing the same active substance as Cystagon, mercaptamine.

Nonclinical studies have been provided for this application and considered sufficient. From a clinical perspective, this application contains new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant’s clinical overview on these clinical aspects based on information was considered sufficient.

PROCYSBI gastro-resistant capsule can be administered as hard capsule or its content can be mixed with food or liquid. There bioequivalence studies with cross over design run in healthy volunteers form the basis for approval of the administration methods for PROCYSBI. The study designs were considered adequate to evaluate the bioequivalence of the administration methods. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of PROCYSBI met the protocol-defined criteria for non-inferiority when compared with the Cystagon. The two-sided 95.8% confidence interval was (0.01, 0.15) with the upper limit well below the margin for non-inferiority corresponding to a p-value less than 0.0001. Therapeutic equivalence of the two formulations was demonstrated.

A positive benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, non-clinical, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of PROCYSBI in the treatment of proven nephropathic cystinosis is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack targeting all physicians who are expected to prescribe PROCYSBI prior to the launch.

The education pack is aimed at strengthening awareness of important identified and potential risks as well as appropriate patient selection, the need for dose titration and patient monitoring.

The physician education pack should contain the Safety Checklist, the Summary of Product Characteristics and Package Leaflet.

The Safety Checklist should highlight the following:

- The risk of teratogenicity and relevant risk minimisation advice:
    - Women of childbearing potential should be informed about the risk of teratogenicity;
    - For women of child-bearing potential a negative pregnancy test should be confirmed before starting treatment;
    - Women of child-bearing potential should be advised to use an adequate method of contraception during the course of treatment;
    - Women of child-bearing potential should be advised to alert the treating physician if they become pregnant during treatment.

- The risk of fibrosing colonopathy and relevant risk minimisation advice:
    - Patients should be informed about the potential risk of fibrosing colonopathy;
    - Patients should be advised of the signs and symptoms of fibrosing colonopathy and to alert the treating physician if they develop any.
- Guidance on appropriate patient selection and dose titration.
- The need for monitoring of white blood cell cysteine levels, full blood count and liver function.
- The need to monitor regularly skin and to consider X-ray examinations of the bone as necessary.
- The need to advise patients about:
    - The method of administration and timing of medicine intake
    - The need to contact the treating physician if they experience the following events:
        - ✓ Problems or changes with their skin
        - ✓ Upset in their normal bowel habit,
        - ✓ Lethargy, somnolence depression, fits
        - ✓ Any suspicion that they might be pregnant

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational pack.

Conditions or restrictions with regard to the safe and effective use of the

medicinal product to be implemented by the Member States.

Not applicable.