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CADTH COMMON DRUG REVIEW

# Clinical Review Report

## Cysteamine delayed-release capsules (Procysbi)

Horizon Pharma Ireland Ltd.

Indication: For the treatment of nephropathic cystinosis


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| Service Line: | CADTH Common Drug Review |
| Version: | Final |
| Publication Date: | February 2018 |
| Report Length: | 67 Pages |

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**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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# Abbreviations

| | |
|---|---|
| **AE** | adverse event |
| **BMI** | body mass index |
| **BSA** | body surface area |
| **CDR** | CADTH Common Drug Review |
| **CI** | confidence interval |
| **CSR** | Clinical Study Report |
| **CTNS** | cystinosin, lysosomal cystine transporter |
| **eGFR** | estimated glomerular filtration rate |
| **ESRD** | end-stage renal disease |
| **HRQoL** | health-related quality of life |
| **ITT** | intent-to-treat |
| **LSM** | least squares mean |
| **MCID** | minimal clinically important difference |
| **PedsQL 4.0** | Pediatric Quality of Life Inventory version 4.0 |
| **PPI** | proton pump inhibitor |
| **RCT** | randomized controlled trial |
| **SAE** | serious adverse event |
| **SD** | standard deviation |
| **SE** | standard error |
| **SF-36** | Short Form 36 |
| **ULN** | upper limit of normal |
| **VAS** | visual analogue scale |
| **WBC** | white blood cell |
| **WDAE** | withdrawal due to adverse event |

| | |
|---|---|
| **Drug** | Cysteamine delayed-release capsules (Procysbi) |
| **Indication** | Treatment of nephropathic cystinosis |
| **Reimbursement Request** | As per indication |
| **Dosage Form(s)** | Delayed-release 25 mg and 75 mg capsules |
| **NOC Date** | 13 June 2017 |
| **Manufacturer** | Horizon Pharma Ireland Ltd. |

# Executive Summary

## Introduction

Cystinosis is a rare autosomal recessive metabolic disease, caused by mutations in the cystinosin, lysosomal cystine transporter (CTNS) gene.[1] These mutations cause a defect in cystinosin transport of cystine out of the lysosome, resulting in an accumulation of cystine in all organs with initial manifestation in the kidney.[1,2] Renal symptoms include the appearance of severe Fanconi syndrome or tubulopathy that later progresses to chronic kidney disease, where renal replacement therapy of choice is kidney transplantation.[1] Ocular symptoms are characterized by cystine crystal deposits in the cornea, which can result in photophobia and reductions in visual acuity.[1,3] Other manifestations can include growth retardation, irregular retinal depigmentation, rickets, hepatomegaly, hypothyroidism, insulin-dependent diabetes, muscular weakness, neurocognitive abnormalities, bone fractures, and infertility.[1-3] Cystinosis is classified into three different subtypes based on severity of the CTNS gene mutation;[3] infantile nephropathic form, juvenile nephropathic form, and adult non-nephropathic. The infantile nephropathic form is the most serious form and the most prevalent, implicated in 95% of cases.[1,3]

Management of nephropathic cystinosis currently consists of both symptomatic treatment and specific treatment with cysteamine. Therapy with oral cysteamine is used to preserve renal function and reduce extrarenal complications. It is often started at the time of diagnosis of cystinosis and continued lifelong.[4]

Procysbi (delayed-release cysteamine) is indicated for the treatment of nephropathic cystinosis and is available in 25 mg and 75 mg oral capsules. The recommended maintenance dose for cysteamine-naive patients is 1.30 g/m$^2$ per day, divided into two equal doses given every 12 hours.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of delayed-release cysteamine (Procysbi [RP103]).

## Results and Interpretation

### Included studies

One study met the inclusion criteria for this review. Study RP103-03 (N = 43) was a randomized, crossover, open-label study evaluating the noninferiority of RP103 (enteric-

coated, delayed-release cysteamine) with Cystagon (immediate-release cysteamine). Patients were greater than and equal to 6 years old, had nephropathic cystinosis, and were on a stable dose of Cystagon sufficient to maintain their white blood cell (WBC) cystine level at less than and equal to 2.0 nmol half cystine/mg protein. Randomization was preceded by a two- to three-week run-in period during which all patients received Cystagon every six hours. There were two treatment periods of three weeks each, with no washout period between treatments. The primary outcome of the study was mean peak WBC cystine levels. Noninferiority testing of RP103 compared with Cystagon was based on WBC cystine levels.

There were several weaknesses in the study design. The study was not blinded, and while the justification for not using blinded methodology was reasonable, the lack of blinding could have introduced bias into the assessment of subjective outcomes such as health-related quality of life and adverse events. Furthermore, the reasons for selecting a noninferiority margin of 0.3 nmol half cystine/mg protein did not appear to be based upon the minimal clinically important difference. The minimal clinically important difference for WBC cystine has not been established (Appendix 4b). The impact of a difference smaller than the noninferiority margin on clinical outcomes is not known.

### Efficacy

No data were available for some outcomes listed in the review protocol, specifically: patient growth, time to renal transplant, kidney function, growth hormone usage, cognitive function, impact on thyroid function, pulmonary dysfunction, incidence of myopathy, cholesterol levels, retinopathy, vascular/cerebral calcifications, glucose control, and hypergonadotropic hypogonadism.

No patients died during the study. Health-related quality of life (HRQoL) was measured using the PedsQL 4.0 Core Scale. There was no statistical testing performed on the data and there were no obvious differences observed between the two treatments. In the per-protocol population, the least squares mean for WBC cystine at week 3 in the RP103 and Cystagon groups were 0.52 and 0.44 nmol half cystine/mg protein, respectively (mean difference: 0.08; 95.8% confidence interval [CI], 0.012 to 0.15; $P < 0.001$). In the intent-to-treat (ITT) population, the least squares mean for WBC cystine at week 3 in the RP103 and Cystagon groups were 0.53 and 0.74 nmol half cystine/mg protein, respectively (mean difference: –0.21; 95.8% CI, –0.48 to 0.06; *P* value not reported).The upper limit of the 95.8% confidence interval was lower than the noninferiority margin of 0.3 nmol half cystine/mg protein in the per-protocol and the ITT analyses. There were no clinically significant differences observed between the two treatments for kidney function, adherence to therapy, or swallowing difficulties, but the study was not designed to detect differences in these outcomes.

### Harms

Overall, 58% and 32% of patients reported adverse events during treatment with RP103 and Cystagon, respectively. Gastrointestinal adverse events were the most frequently reported category of adverse event and were reported in 14 patients (33%) during treatment with RP103 and in nine patients (22%) during treatment with Cystagon. Of the more frequently reported adverse events, patients reported nausea (16%), vomiting (19%), and abdominal pain (9%) during treatment with RP103, compared with 7%, 12%, and 0%, during treatment with Cystagon, respectively. The incidence of non-gastrointestinal adverse events in the study was 26% during treatment with RP103 and the incidence was 10% during treatment with Cystagon.

## Potential Place in Therapy

The clinical expert consulted for the review noted that, based on its design, included outcomes, and limited statistical comparisons, the RP103-03 study really only addresses the reduction of whole WBC cystine levels. The observed effect with Procysbi relative to Cystagon in the study likely indicates that Procysbi has a clinically meaningful effect in reducing cystine levels, similar to that of Cystagon; however, there remains uncertainty about the relative effects of Procysbi on other outcomes.

## Conclusions

Results of a small crossover randomized controlled trial (RCT) indicated that Procysbi (RP103) is noninferior to Cystagon based on WBC cystine levels after three weeks of open-label treatment. A noninferiority boundary of 0.3 nmol half cystine/mg protein was selected, but the minimal clinically important change in WBC cystine is not known. There were no clinically significant differences observed between the two cysteamine formulations for other outcomes such as adherence to therapy, swallowing ability, or quality of life, but the trial was not designed to show differences in these outcomes. The rates of serious adverse events, as well as non-serious gastrointestinal and non-gastrointestinal adverse events, were higher during treatment with Procysbi compared with the rates observed during treatment with Cystagon.

### Table 1: Summary of Efficacy Results — WBC Cystine Levels

| Population | Treatment | N | LSM (SE) | Difference of LSM (SE) | 95.8% CI of LSM Difference | *P* Value |
|---|---|---|---|---|---|---|
| **Per-Protocol** | Cystagon | 39 | 0.44 (0.06) | 0.08 (0.03) | 0.01 to 0.15 | < 0.0001 |
| | RP103 | 39 | 0.52 (0.06) | | | |
| **Intent-to-Treat** | Cystagon | 41 | 0.74 (0.14) | –0.21 (0.13) | –0.48 to 0.06 | NR |
| | RP103 | 43 | 0.53 (0.14) | | | |

CI = confidence interval; LSM = least squares mean; NR = not reported; SE = standard error.

Source: FDA Medical Review[5] Clinical Study Report.[6]

## Table 2: Summary of Harms in Study RP103-03

| | Treatment Period | | | |
|---|---|---|---|---|
| **Parameter** | **Run-In N = 43** | **RP103 N = 43** | **Cystagon N = 41** | **Overall N = 43** |
| **Patients with ≥ 1 AE, n(%)** | **13 (30)** | **25 (58)** | **13 (32)** | **34 (79)** |
| AE with overall incidence ≥ 5% | | | | |
| Vomiting | 3 (7) | 8 (19) | 5 (12) | 14 (33) |
| Nausea | 1 (2) | 7 (16) | 3 (7) | 10 (23) |
| Abdominal pain | 4 (9) | 4 (9) | 0 | 8 (19) |
| Headache | 2 (5) | 4 (9) | 0 | 5 (12) |
| Decreased appetite | 0 | 1 (2) | 2 (5) | 3 (7) |
| Hypokalemia | 0 | 3 (7) | 0 | 3 (7) |
| Cough | 1 (2) | 2 (5) | 0 | 3 (7) |
| Rhinorrhea | 3 (7) | 0 | 0 | 3 (7) |
| Renal impairment | 0 | 2 (5) | 1 (2) | 3 (7) |
| **Patients with ≥ 1 SAE, n(%)** | **0** | **6 (14)** | **1 (2)** | **7 (16)** |
| Abdominal discomfort | 0 | 1 (2) | 0 | 1 (2) |
| Vomiting | 0 | 1 (2) | 0 | 1 (2) |
| Hypokalemia | 0 | 1 (2) | 0 | 1 (2) |
| Hypovolemia | 0 | 0 | 1 (2) | 1 (2) |
| Gastroenteritis | 0 | 1 (2) | 0 | 1 (2) |
| Femur fracture | 0 | 1 (2) | 0 | 1 (2) |
| Knee deformity | 0 | 1 (2) | 0 | 1 (2) |
| **Patients with ≥ 1 AE leading to discontinuation, n(%)** | 0 | 1 (2) (*cellulitis*) | 0 | 1 (2) |

AE = adverse event; N = total number of patients; n = number of patients in subgroup; SAE = serious adverse event.

Source: Clinical Study Report.[6]

# Introduction

## Disease Prevalence and Incidence

Cystinosis is a rare autosomal recessive metabolic disease, caused by mutations in the cystinosin, lysosomal cystine transporter (CTNS) gene.[1] These mutations cause a defect in cystinosin transport of cystine out of the lysosome, resulting in an accumulation of cystine in all organs, with initial manifestation in the kidney and eye.[1,2] Renal symptoms include the appearance of severe Fanconi syndrome or tubulopathy that later progresses to chronic kidney disease, where renal replacement therapy of choice is kidney transplantation.[1] Ocular symptoms are characterized by cystine crystal deposits in the cornea, which can result in photophobia and reductions in visual acuity.[1,3] Other manifestations can include growth retardation, irregular retinal depigmentation, rickets, hepatomegaly, hypothyroidism, insulin-dependent diabetes, muscular weakness, neurocognitive abnormalities, bone fractures, and infertility.[1-3]

Cystinosis is classified into three different subtypes based on the severity of the CTNS gene mutation:[3] infantile nephropathic form, juvenile nephropathic form, and adult non-nephropathic form. The infantile nephropathic form is the most serious form and the most prevalent, implicated in 95% of cases.[1,3] Symptoms of this form generally present before the age of 12 months, with evidence of proximal tubular damage with or without corneal cystine crystal deposits.[7] There is further organ involvement as the disease progresses.[7] Juvenile nephropathic cystinosis carries similar symptoms to infantile cystinosis, except its onset is delayed to within the first decade of life, and it carries a slower progression rate.[3] The adult non-nephropathic form of cystinosis is exclusively ocular, with photophobia due to corneal crystals.[1] Patients very often identify this disease as having a serious impact on their school and work life, and also admit that it takes a toll on the entire family. Many parents of children with cystinosis have reported that it requires 24/7 vigilance, with the combination of regular clinic and allied health professional visits.

The prevalence of cystinosis is approximately 1 in 100 000 to 1 in 200 000 births globally, regardless of ethnic origin.[8] A higher incidence rate has been observed in selected populations with detected founder mutation in the province of Brittany, France (1 in 26,000 live births) as well as in Saguenay–Lac-Saint-Jean, Quebec (1 in 62,500 live births).[3,9]

Upon findings of renal tubular Fanconi's syndrome, nephropathic cystinosis should be investigated among other inherited causes.[4] It is subsequently confirmed by findings of: corneal cystine crystals on slit lamp examination, increased cystine content of leukocytes, and CTNS mutations.[4] Other indicators that can identify disease progression include impaired growth, anorexia, reduction in glomerular filtration rate leading to chronic kidney disease, hypothyroidism, metabolic bone disease, swallowing difficulties, delayed gastric emptying and intestinal dysmotility, hypocholesterolemia, and neurocognitive alterations in attention, planning, and motor processing speed.[1,4,8]

## Standards of Therapy

In nephropathic cystinosis, lysosomal cystine accumulation damages different tissues at different rates, perhaps by enhancing apoptosis.[8] Therefore, management of nephropathic cystinosis currently consists of both symptomatic treatment and specific treatment with cysteamine.

The aim of symptomatic treatment is to maintain fluid and electrolyte balance, encourage good nutrition, and prevent rickets. Due to impaired sweating in these patients, heat exhaustion is a concern. The loss of excessive water and salts in the urine can lead to dehydration as well as progression to acidosis.[8] As a result, patients are often provided with supplementary doses of potassium, sodium, and phosphate, in accordance with serum values. Other symptoms such as poor appetite, vomiting, and oral motor dysfunction can be circumvented by the use of a nasogastric or gastronomy tube.[4] For impairment in growth velocity, patients with nephropathic cystinosis can be administered growth hormone to improve and maintain velocity.[10]

For all nephropathic cystinosis patients, early and diligent cystine-depleting therapy with oral cysteamine is recommended to preserve renal glomerular function. Administration of cysteamine has been found to prevent further deterioration of renal function and development of renal complications, as well as extrarenal complications.[11-13] As a result, cysteamine is recommended to be administered at the time of diagnosis of cystinosis, and continued lifelong.[4]

## Drug

Delayed-release cysteamine (Procysbi) capsules are a beaded, enteric-coated, delayed-release formulation of the bitartrate salt of cysteamine (also called cysteamine bitartrate or mercaptamine bitartrate), which reacts with lysosomes to convert intracellular cystine to cysteine, which is able to exit the lysosome.[5,14] This reduces accumulation of lysosomal cystine as a result of the defective transport of this molecule in cystinosis patients.[3,5,14] This formulation is encapsulated in hard gelatin, and to be administered orally.[5] Capsules can be opened and the contents either sprinkled on food or dispersed in liquids, and the medication can also be administered via gastrostomy, nasogastric, or gastrostomy-jejunostomy tube.[15]

The enteric-coated capsule dissolves rapidly in the stomach, however the microspheronized beads within the capsule do not dissolve until they reach the small intestine, which is intended to reduce gastrointestinal adverse effects and improve bioabsorption.[15] This formulation results in stable plasma cysteamine levels over 12 hours, which enables twice-daily dosing, and eliminates the need for nighttime administration.[15]

The immediate-release form of cysteamine (Cystagon) had been the primary cystine-depleting therapy accessible in Canada for the treatment of the nephropathic cystinosis. Cystagon was accessed only through Health Canada's Special Access Programme; it did not have a Health Canada Notice of Compliance for the treatment of nephropathic cystinosis. Phosphocysteamine (a phosphorothioester that was developed to be more tolerable and to have fewer adverse effects than cysteamine) was also only accessible through the Special Access Programme. However, according to the clinical expert consulted for this review, phosphocysteamine had the same dosing regimen as immediate-release cysteamine and was used less frequently than Cystagon. Both immediate-release products became inaccessible during the course of the CDR review after Procysbi became available on the market in Canada.

## Table 3: Key Characteristics of Procysbi and Cystagon

| | Procysbi | Cystagon[a] |
|---|---|---|
| **Mechanism of Action** | Aminothiol converting cysteine into cysteine and cysteine-cysteamine mixed disulfides, reducing lysosomal cystine crystal accumulation | |
| **Indication[b]** | Treatment of nephropathic cystinosis | |
| **Route of Administration** | Oral (delayed-release capsules) | Oral (immediate-release capsules) |
| **Recommended Dose** | Maximum dose: 1.95 g/m$^2$/day in divided doses, administered every 12 hours.<br><br>Available doses: 25 mg, 75 mg | Maximum dose: 1.95 g/m$^2$/day in divided doses, administered every 6 hours.<br><br>Available doses: 50 mg, 150 mg |
| **Serious Side Effects / Safety Issues** | Gastrointestinal adverse effects, halitosis, bad (sulphurous) odour | |

[a] Cystagon was available through the Health Canada Special Access Programme and has not been approved for marketed use.

[b] Health Canada indication.

Source: Product Monograph.[15]

# Objectives and Methods

## Objectives

To perform a systematic review of the beneficial and harmful effects of cysteamine delayed-release capsules (Procysbi; 25 mg and 75 mg) for the treatment of nephropathic cystinosis in children and adults.

## Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 4.

### Table 4: Inclusion Criteria for the Systematic Review

| | |
|---|---|
| **Patient Population** | Adults and children with nephropathic cystinosis |
| **Intervention** | Cysteamine delayed-release capsules (25 mg and 75 mg) |
| **Comparators** | • Immediate-release cysteamine<br>• Phosphocysteamine<br>• Placebo<br>• No treatment |
| **Outcomes** | **Key efficacy outcomes:**<br>• Survival[a]<br>• QoL[a]<br>• Patient growth[a]<br>• Time to ESRD or renal transplant<br>**Other efficacy outcomes:**<br>• Proton pump inhibitor usage<br>• Cystine in peripheral WBC<br>• Kidney function[a]<br>• Adherence to therapy[a]<br>• Initiation of growth hormone, growth hormone dose change<br>• Cognitive function, hypothyroidism, pulmonary dysfunction, swallowing abnormalities, myopathy, hypercholesterolemia, retinopathy, vascular/cerebral calcifications, diabetes mellitus, hypergonadotropic hypogonadism<br>**Harms outcomes:**<br>• Adverse events[a]<br>• Serious adverse events[a]<br>• WDAEs<br>Adverse events of interest: gastrointestinal (e.g., ulceration or bleeding, nausea, vomiting), neurological (e.g., seizure, lethargy, somnolence, benign intracranial hypertension)[a] |
| **Study Design** | Published and unpublished RCTs |

[a] Refers to outcomes that were noted in the patient input.

ESRD = end-stage renal disease; QoL = quality of life; RCT = randomized controlled trial; WBC = white blood cells; WDAE = withdrawal due to adverse events.

Source:

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946– ) with in-process records and daily updates via Ovid; Embase (1974– ) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Procysbi, delayed action, and cystinosis.

No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on September 9, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on December 13, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Drug and Device Regulatory Approvals; Advisories and Warnings; and Drug Class Reviews. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

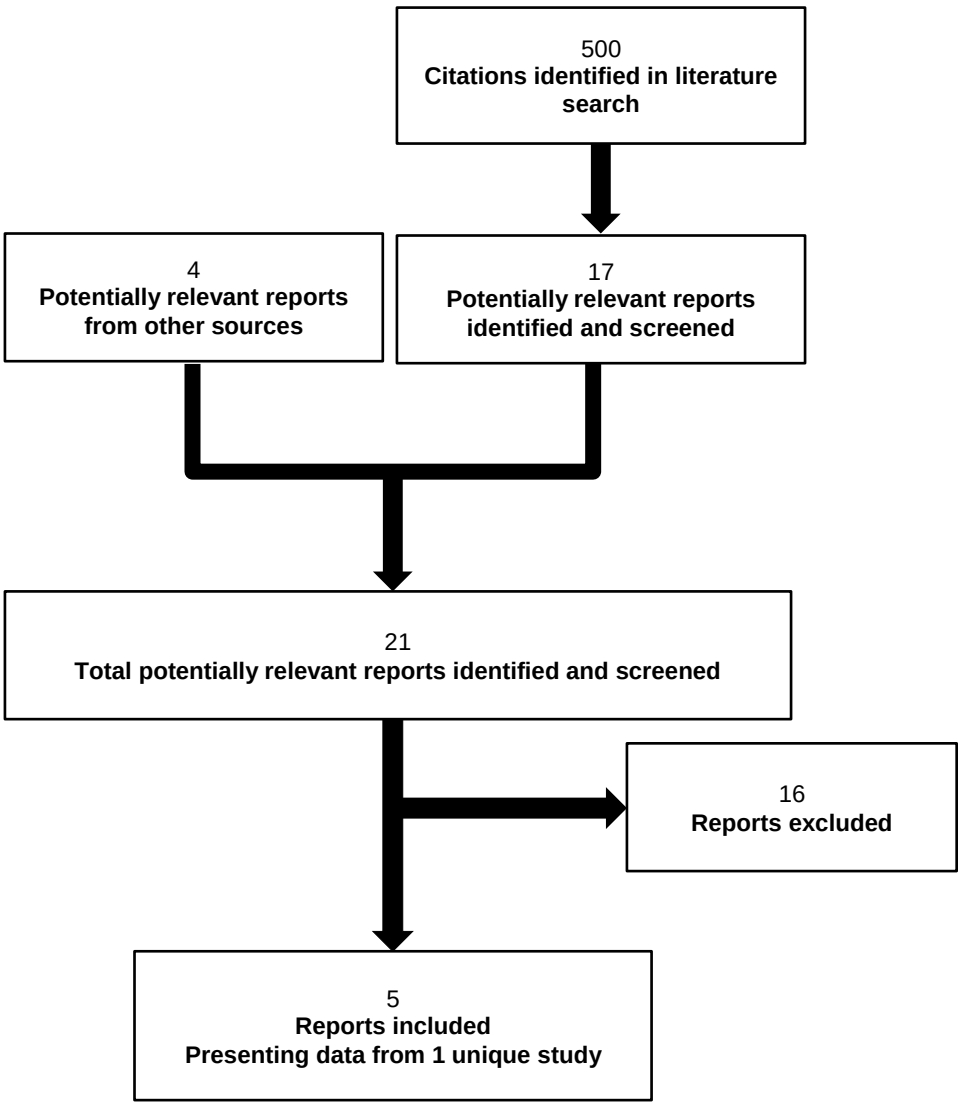
Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

# Results

## Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 5. A list of excluded studies is presented in Appendix 3.

### Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



## Table 5: Details of Included Study

| | | RP103-03 |
|---|---|---|
| Design and Population | **Study Design** | Open-label, randomized, crossover, noninferiority |
| | **Locations** | 8 sites in total: France, Netherlands, US |
| | **Randomized (N)** | 43 (ITT population) |
| | **Inclusion Criteria** | • Documented diagnosis of nephropathic cystinosis<br>• On stable dose of Cystagon sufficient to maintain their WBC cystine level at ≤ 2.0 nmol half cystine/mg protein<br>• Able to swallow Cystagon capsule intact<br>• Within the last 6 months, no clinically significant change from normal in LFTs (i.e., 1.5 times ULN for ALT and AST, and/or 1.5 times ULN for total bilirubin) and renal function |
| | **Exclusion Criteria** | • < 6 years old or weight < 21 kg<br>• Current history of: inflammatory bowel disease 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<br>• Hemoglobin < 10 g/dL at screening or any unsafe level<br>• Received any form of cysteamine medication through a gastric tube<br>• Receiving maintenance dialysis or has had a kidney transplant<br>• On active kidney transplant list or planning to receive transplant within 3 months of screening |
| Drugs | **Intervention** | RP103 q.12.h. (enteric-coated, delayed-release cysteamine bitartrate) |
| | **Comparator(s)** | Cystagon q.6.h. (immediate-release cysteamine bitartrate) |
| Duration | **Phase** | |
| | Run-in | 2 weeks open-label |
| | Period 1 (pre-crossover) | 3 weeks open-label |
| | Period 2 (post-crossover) | 3 weeks open-label |
| | Extension | 2 years open-label RP103 only (separate study, see Appendix 6) |
| Outcomes | **Primary End Point** | WBC cystine levels using repeated measurements at steady state cysteamine trough.<br>Period 1: Days 5, 6,and 7 of week 6<br>Period 2: Days 5, 6,and 7 of week 9<br>Noninferiority margin: 0.3 nmol half cystine/mg protein |
| | **Other End Points** | Quality of Life<br>Impact on swallowing<br>Pharmacokinetics<br>PPI usage |
| Notes | **Publications** | Langman 2012[16] |

Note: 4 additional reports were included (FDA Medical Report[5] FDA Statistical Report[14] Manufacturer's submission[17] Clinical Study report[6] ).

ALT = alanine transaminase; AST = aspartate transaminase; LFT= liver function test; N = total number of patients; PPI = proton pump inhibitor; q.6.h. = every 6 hours; q.12.h. = every 12 hours; ULN= upper limit of normal; WBC = white blood cell.

Source: Clinical Study Review.[6]

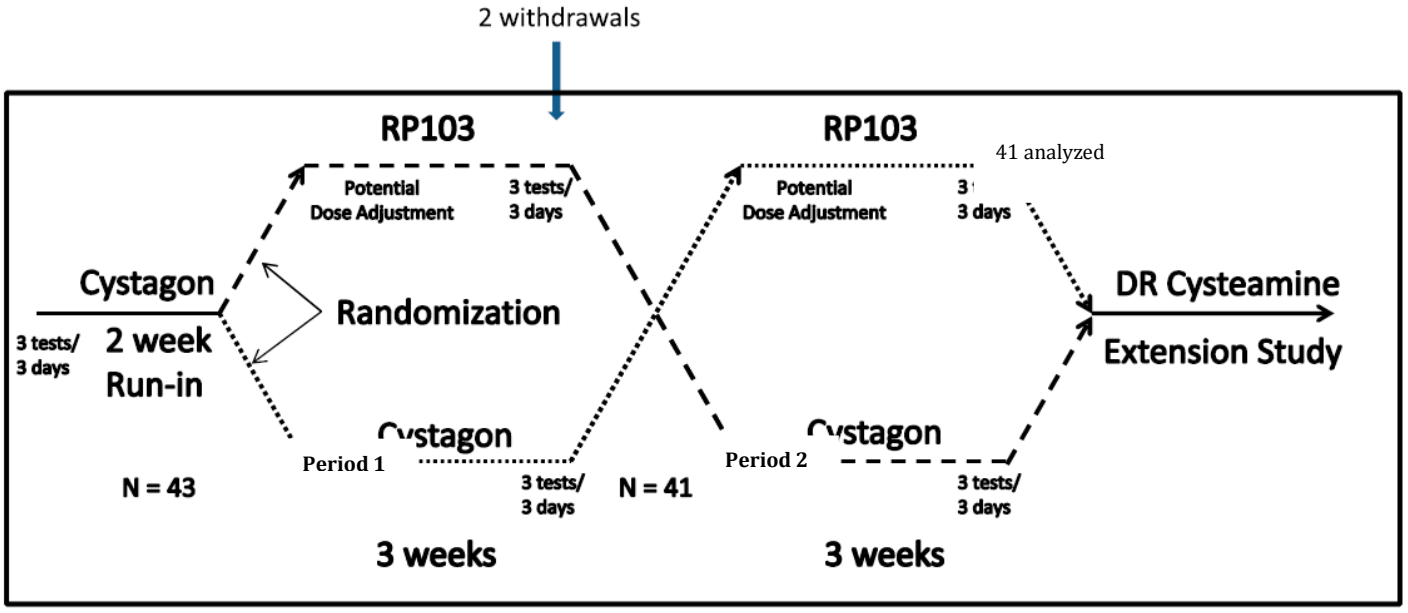
## Included Studies

### Description of studies

One noninferiority study met the inclusion criteria for this report and is summarized in Table 5. Study RP103-03 was a randomized, crossover, open-label study evaluating the noninferiority of RP103 (enteric-coated, delayed-release cysteamine) with Cystagon (immediate-release cysteamine). Randomization was preceded by a two- to three-week run-in period in which all patients received Cystagon every six hours (Figure 1). There were two treatment periods of three weeks each. There was no washout period between Period 1 and Period 2. Patients immediately crossed over to the alternative treatment at the end of Period 1. A washout period was deemed not necessary because of the short half-life and dosing regimen of each treatment: RP103 every 12 hours (mean half-life of 5.85 hours); Cystagon every six hours (mean half-life of 1.90 hours).[14]

Following Period 2, patients were offered enrolment in a long-term open-label follow-up study in which they received RP103 every 12 hours (see Appendix 6).

## Figure 2: RP103-03 Study Design




DR = delayed-release; N = total number of patients in study.

Source: CDR Submission[17]

### Populations

*Inclusion and exclusion criteria*

Adults and children with a documented diagnosis of nephropathic cystinosis were included in the study if they were able to swallow Cystagon tablets intact. They must have been on a stable dose of Cystagon considered by the investigator to be sufficient for maintaining the WBC cystine level at less than and equal to 2.0 nmol half cystine/mg protein. Patients must

have had their own kidneys and adequate renal function (estimated glomerular filtration rate [eGFR] greater than 30 mL/min/1.73m$^2$ body surface area).[6,16]

*Baseline characteristics*

The ITT population was predominantly Caucasian (42/43 patients).[6] The age range was six years to 26 years with 84% of patients under 16 years old.[6] The average age was approximately 12 years. The only adult patient (greater than 21 years) was a 26-year-old female.[6] The baseline characteristics are presented in Table 6. There were no important imbalances observed between the groups randomized to the two different treatment sequences (data not shown).[14] There was a larger proportion of adolescents aged 13 years to 17 years randomized to the Cystagon→RP103 sequence (10/22 patients) compared with the RP103→Cystagon sequence (3/22 patients), but this is not expected to introduce bias to the results.[14]

## Table 6: Summary of Baseline Characteristics in Study RP103-03

| | Intent-to-Treat Population | Per-Protocol Population |
|---|---|---|
| N | 43 | 39 |
| Mean age (SD), years | 11.7 (4.2) | 11.9 (4.3) |
| Age 2 to ≤ 12, n | 27 | NR |
| Age 12 to ≤ 21, n | 15 | NR |
| Age > 21, n | 1 | NR |
| From US | 26 (60) | NR |
| From Europe | 17 (40) | NR |
| Male, n(%) | 24 (56) | 23 (59) |
| Mean height (SD), cm | 140 (19) | 140 (20) |
| Mean weight (SD), kg | 36 (14) | 36 (15) |
| Mean BMI (SD), kg/m$^2$ | 18 (3) | 18 (3) |
| Mean BSA (SD), m$^2$ | 1.2 (0.3) | 1.2 (0.3) |
| Mean Cystagon dose, mg/day | 1,849 (546) | 1,832 (539) |
| Mean Cystagon dose, mg/kg/day | 56 (15) | NR |
| Mean WBC cystine during run-in period, nmol half cystine/mg protein (SD) | 0.66 (0.34) | 0.49 (0.26) |
| WBC cystine < 1 nmol half cystine/mg protein during run-in period, n(%) | 37 (86) | 37 (95) |

BMI = body mass index; BSA = body surface area;; n = number of patients in subgroup; nmol = nanomoles; NR = not reported; SD = standard deviation; WBC = white blood cell.

Source: Langman et al.; FDA Statistical Review, Clinical Study Report .[6,14,16]

### Interventions

At the end of the run-in period and prior to the start of Period 1, patients were randomized to one of two open-label treatment sequences; three weeks (± 3 days) treatment with Cystagon every six hours followed by crossover to three weeks (± 3 days) of RP103 every 12 hours or the reverse sequence (RP103 followed by crossover to Cystagon). Qualifying patients were stratified based on their level of WBC cystine during the run-in period (Group L: ≤ 1.0 nmol half cystine/mg protein; Group H: > 1.0 ≤ 2.0 nmol half cystine/mg protein) then randomized to one of the two treatment sequences.[6] Patients randomized to Cystagon received their usual dose every six hours and patients randomized to RP103 received a daily dose (divided into doses every 12 hours) of RP103 approximately equal to 70% of their usual Cystagon dose.[16]

Patients 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 less than and equal to 2.0 nmol half cystine/mg protein. 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. Following a protocol amendment, the starting dose regimen for newly enrolled patients receiving RP103 was 80% of their end of run-in period total daily Cystagon dose. An RP103 dose increase to 100% of their end of run-in 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.[6]

### *Concomitant therapy*

Patients were permitted to continue taking medications to reduce gastric acid while receiving Cystagon, but not while receiving RP103. Patients were required to stop taking proton pump inhibitors (PPIs) and other gastric acid-reducing drugs at least 12 hours before beginning treatment with RP103. All other concomitant medications were continued unchanged during both periods of the study.[16]

## Outcomes

The primary efficacy outcome was WBC cystine levels: repeated measurements during days 5, 6, and 7 of week 6 (Period 1) and week 9 (Period 2) for Cystagon and RP103, at 0 hours under Cystagon and at 0.50 hours under RP103, in a crossover design. These time points correspond to the trough of cysteamine concentration.[6]

Other outcomes planned for the study were:

- Quality of life (Pediatric Quality of Life Inventory version 4.0 Generic Core Scales [PedsQL 4.0], Short Form 36 [SF-36])
- Visual analogue scale (VAS) for swallowing
- Usage of drugs to reduce gastric acid
- Pharmacokinetic parameters (Tmax, AUC, Cmax for cysteamine)
- Pharmacodynamic parameters (WBC cystine concentrations)
- Treatment compliance
- Adverse events

See Appendix 4 and 4b for a description of the PedsQL 4.0 and SF-36, VAS for swallowing, and WBC cystine.

## Statistical analysis

### *Sample size estimation*

The sample size was estimated to be between 30 and 50 patients because the manufacturer used a method that would allow for adjustment of the sample size after the first 20 patients. Patients who dropped out of treatment following randomization were included in the sample size re-estimation. The manufacturer specified alpha = 0.02104 for the primary outcome instead of alpha = 0.025 for the sample size re-estimation to be performed at the end of Stage I. This threshold for statistical significance was chosen to achieve 90% power, and

because the sample size increase could inflate the type-1 error of the final analysis. The use of a nominal significance level of 0.02104 for the final analysis guaranteed that the true level of significance will not exceed 0.025 despite this inflation.[6]

### *Noninferiority testing*

The investigators predefined a noninferiority margin of 0.3 nmol half cystine/mg protein for the primary outcome. If the one-sided test of noninferiority, conducted at the nominal level of 0.02104 is rejected at a noninferiority margin of 0.3, it would be concluded that RP103 is noninferior to Cystagon with an overall significance level of 0.025.[6]

### *Analysis populations*

The ITT population (N = 41) was defined as all patients who completed the run-in period and the two 3-week crossover periods. The safety population (N = 43) was defined as all patients who received at least one dose of either Cystagon or RP103, starting with the first day of the run-in period.

The per-protocol population was considered to be the population for the primary outcome analysis. The per-protocol population (N = 39) consisted of all patients from the ITT population excluding patients who had a 3-day average WBC cystine level greater than 2 nmol half cystine/mg protein during one of the periods under Cystagon and were therefore considered as “not well controlled” under Cystagon.[6,16]

## Patient disposition

Of 45 patients who were initially screened, one patient was a screening failure and one additional patient was discontinued before randomization, resulting in 43 patients who were randomized to one of two treatment sequences.[6] One patient discontinued from the study after randomization due to an adverse event (n = 1) related to complications from a planned knee surgery. The second patient who discontinued was a sibling of the aforementioned patient who discontinued the study because of the family’s decision to withdraw both children. An additional two patients did not qualify for the per-protocol population because they had a 3-day average WBC cystine level greater than 2 nmol half cystine/mg protein during one of the periods under Cystagon and therefore were not considered well controlled under Cystagon.[6,16]

As described in Table 7, the ITT population had 43 patients and the per-protocol population had 39 patients. The per-protocol population presented in the main study publication was incorrectly described as having 38 patients.[16] An erratum was published explaining that this was related to an error that occurred during the investigators’ statistical analyses.[18] For this reason, the clinical study report is the main source of the data for the per-protocol population in this CDR report.[6]

## Table 7: Patient Disposition

| | RP103-03 |
|---|---|
| **Screened, N** | 45 |
| **Screened twice, N** | 7 |
| **Screening failures, N** | 1 |
| **Patients enrolled, N** | 44 |
| **Patients enrolled and randomized, N** *(ITT population)* | 43 |
| **Patients randomized and discontinued, n(%)** | 2 (5) |
| **Patients randomized and completed, n(%)** | 41 (95) |
| **Ineligible for inclusion in the per-protocol population, n(%)** | 2 (5) |
| *Per-protocol population, n* | 39 |

ITT = intent-to-treat; N = total number of patients; n = number of patients in subgroup.

Source: Clinical Study Report.[6]

## Exposure to Study Treatments

The mean Cystagon dose during the run-in period was 1,831 mg/day (standard deviation: 539 mg), per-protocol population.[6]

For the 34 patients whose starting dose was approximately 70% of the end total daily dose of Cystagon during the run-in period, 21 (61.8%) had their RP103 dose increased, while 13 (38.2%) remained at their starting dose. Of the nine patients whose starting dose was approximately (or greater than) 80% of the end total daily dose of Cystagon during the run-in period, only three (33.3%) had their RP103 dose increased, while six (66.7%) remained at their starting dose. On average, the total daily, steady state dose of RP103 in patients in the trial was 82% of their established, incoming dose of Cystagon.[6]

## Critical Appraisal

### Internal validity

- The trial was not blinded. This may have introduced bias into the analyses of the outcomes which were subjectively assessed, but the direction of such bias is unknown. The authors of the main publication state several reasons for not blinding, including potential differences in the odour of the cysteamine and placebo products, the obvious impact of cysteamine on breath odour, and the pill swallowing burden that placebo would introduce into a very young population.[14]
- No washout period was given between Period 1 and Period 2. The manufacturer's reasons for not using a washout period were related to the short half-life of Cystagon (1.9 hours) and RP103 (5.85 hours).[14]
- While there were only four patients excluded from the ITT population to form the per-protocol population, this represents a considerable proportion (10%) of the patients enrolled in this study. CDR reviewers noted changes in the results of the primary outcome that were dependent on the exclusion or inclusion of just one patient in the main analysis. When a per-protocol population of 38 was used in the publication for study RP103-03,[16] the mean WBC cystine levels were different, if compared with the results when 39 patients were used.[6] The mean WBC cystine levels at end of study for both cysteamine products changed when one patient was added to the per-protocol population. The overall hypothesis test results for noninferiority were the same, regardless as to whether 38 or 39 patients were used. However, this illustrates the small

sample size of this trial and the high sensitivity of results to just one patient being excluded from the analysis.

- The reasons for selecting a noninferiority margin of 0.3 nmol half cystine/mg protein did not appear to be based on the minimal clinically important difference in WBC cystine, which is not well understood (Appendix 4b). WBC cystine level is a standard approach for measuring response to cysteamine therapy and there is some evidence showing a correlation between WBC cystine levels and renal function in patients with nephropathic cystinosis . However, this association has not been precisely quantified and the impact of a difference smaller than the noninferiority margin, on clinical outcomes, is not known. A meaningful change in a patient's status may occur with a reduction (or increase) in WBC cystine level less than the chosen noninferiority boundary of 0.3 nmol half cystine/mg protein. CDR reviewers noted that FDA, Health Canada, and European Medicines Agency reviewers accepted the noninferiority boundary. CDR reviewers note that it is based upon expected reductions in WBC cystine and it is not based upon expected changes in clinical outcomes. CDR reviewers agree with the Health Canada reviewers' assessment that the selected noninferiority range is a liberal noninferiority margin.[17]
- Gastrointestinal adverse events were reported at a higher rate during treatment with RP103 relative to Cystagon. However, use of gastric acid-reducing medications, including PPIs, was allowed during treatment with Cystagon but restricted to intolerable gastric upset during RP103 treatment. For this reason it is difficult to interpret the increase in gastrointestinal adverse events observed during RP103 treatment. There were 475 episodes of proton pump inhibitor usage during treatment with Cystagon and 70 episodes of PPI therapy with RP103.
- The erratum that was published for the RP103-03 trial indicated that there was a significant error in the analyses of the primary outcome that changed the results of the WBC cystine analysis for the per-protocol population. It does not appear that the corrected analyses were published. This lack of peer review for the primary outcome of the pivotal study is a notable weakness of the study. It is not clear to what degree this analytical error impacted other outcomes in the main publication for the RP103-03 study.[16,18]
- There was no stated target for WBC cystine levels in the study, but the clinical expert for this review stated that cysteamine dose is usually adjusted to achieve WBC cystine less than 1 nmol half cystine/mg protein.
- There were some inconsistencies in reporting of data between the main study publication and the manufacturer's clinical study report. The clinical study report states that there were three adults older than 18 years,(26, 23, and 20 years, respectively), but this does not match the study publication, which states that there was only one patient with age above 21 years.[6,16]

### External validity

- There were no Canadian sites in this study, but the clinical expert involved in the review believed that the baseline characteristics of the patients in the study were reasonably similar to the population of Canadian patients who would be candidates for cysteamine.
- The sites were in France, the US, and the Netherlands. The clinical expert for this review stated that the approaches to treating patients with nephropathic cystinosis are similar in Canada, compared with those three countries.
- At the time of the Procysbi submission to CDR, Cystagon was a relevant comparator in the Canadian context. Cystine-depleting therapy is the only treatment directed at the underlying causal mechanism of cystinosis. Prior to Procysbi, immediate-release cysteamine (Cystagon) was the primary cystine-depleting therapy. In Canada, Cystagon was available only through Health Canada's Special Access Program. There were no available studies that included phosphocysteamine, the other cysteamine product

available through the Special Access Programme. The clinical expert involved in the review noted that most (if not all) patients with nephropathic cystinosis were receiving Cystagon at the time this review was conducted.

- The clinical expert for this review stated that the doses used in the RP103-03 study are similar to the doses of cysteamine that would be used in the Canadian context.
- The RP103-03 study had very limited goals and exposure to both medications was short and therefore did not provide information regarding the key efficacy or harms outcomes identified in the Clinical Review protocol of RP103 relative to Cystagon. The study was designed to test noninferiority based on a surrogate outcome (WBC cystine). Some clinical outcomes and patient reported outcomes were collected in the study, but the study was not powered to test superiority or noninferiority for these outcomes.

## Efficacy

Only those efficacy outcomes identified in the review protocol are reported below in Table 8

No data were available for some outcomes listed in the review protocol, specifically: patient growth, time to renal transplant, kidney function, growth hormone usage, cognitive function, impact on thyroid function, pulmonary dysfunction, incidence of myopathy, cholesterol levels, retinopathy, vascular/cerebral calcifications, glucose control, and hypergonadotropic hypogonadism.

### Survival

No patients died during the study.

### Health-related quality of life

Quality of life was measured in the study using the PedsQL 4.0 for the children in the study (n = 36) and the SF-36 was used for patients whose age was greater than 18 years (n = 3). Quality of life data from the adults was not analyzed because there were data from only three adults using the SF-36 instrument.[5]

The pediatric data are presented in Table 8 in three age cohorts: ages 5 years to 7 years, ages 8 years to 12 years, and ages 13 years to 18 years. The values at the end of the run-in treatment period were lower than what would be expected for healthy children (score approximately 84 for healthy children). No statistical comparisons were provided by the manufacturer for the PedsQL 4.0 data. There were no clear patterns of increase or decrease in PedsQL 4.0 values during the course of the study. The minimal clinically important difference is not known for this scale.

## Table 8: PedsQL 4.0 Generic Core Scale Scores During Run-In and Treatment Periods

| Age Cohort | PedsQL 4.0 Scores (0-100 scale) | | | | |
|---|---|---|---|---|---|
| | End of Run-in Period | End of Period 1 | | End of Period 2 | |
| | | Cystagon | RP103 | Cystagon | RP103 |
| 5-7 years<br>N<br>Mean (±SD)<br>Median,<br>Min,Max | <br>N=8<br>75 ± 24<br>75<br>(28, 100) | <br>N=3<br>74 ± 36<br>91<br>(33, 98) | <br>N=4<br>77 ± 20<br>75<br>(56, 100) | <br>N=5<br>78 ± 17<br>70<br>(63, 100) | <br>N=2<br>62 ± 51<br>62<br>(26, 98) |
| 8-12 years<br>N<br>Mean (±SD)<br>Median,<br>Min,Max | <br>N=13<br>79 ± 13<br>82<br>(50, 96) | <br>N=5<br>73 ± 14<br>65<br>(59, 90) | <br>N=9<br>85 ± 11<br>86<br>(61, 99) | <br>N=5<br>86 ± 9<br>86<br>(75, 99) | <br>N=6<br>74 ± 14<br>71<br>(61, 97) |
| 13-18 years<br>N<br>Mean (±SD)<br>Median,<br>Min,Max | <br>N=14<br>75 ± 13<br>76<br>(51, 91) | <br>N=11<br>76 ± 12<br>76<br>(54, 95) | <br>N=3<br>84 ± 18<br>93<br>(64, 96) | <br>N=4<br>86 ± 12<br>86<br>(72, 100) | <br>N=10<br>78 ± 14<br>81<br>(59, 95) |

Source: FDA Medical Review.[5]

### WBC cystine levels

WBC cystine levels were used to assess the primary outcome for study RP103. In the per-protocol population, the least squares mean values for RP103 and Cystagon were 0.52 and 0.44 nmol half cystine/mg protein, respectively, with a difference (standard error) of 0.08 (0.03) nmol half cystine/mg protein ($P < 0.001$). In the intent-to treat population, the least squares mean values for Cystagon and RP103 were 0.74 and 0.53 nmol half cystine/mg protein, respectively, with a difference (standard error) of –0.21 (0.13) nmol half cystine/mg protein. The upper limit of the 95.8% confidence intervals was lower than the noninferiority margin of 0.3 nmol half cystine/mg protein in the per-protocol and the ITT analyses.

## Table 9: WBC Cystine Levels

| Population | Treatment | N | LSM (SE)[a] | Difference of LSM (SE)[a] | 95.8% CI of LSM Difference[a] | *P* Value |
|---|---|---|---|---|---|---|
| Per-Protocol | Cystagon | 39 | 0.44 (0.06) | 0.08 (0.03) | 0.01 to 0.15 | <0.0001 |
| | RP103 | 39 | 0.52 (0.06) | | | |
| Intent-to-Treat | Cystagon | 41 | 0.74 (0.14) | –0.21 (0.13) | –0.48 to 0.06 | NR |
| | RP103 | 43 | 0.53 (0.14) | | | |

CI = confidence interval; LSM = least squares mean; N = total number of patients; NR = not reported; SE = standard error.

[a] Units: nmol half cystine/mg protein.

Source: FDA Medical Review[5] Clinical Study Report.[6]

### Kidney function

There were two patients (5%) with renal impairment and one patient (2%) with renal failure during treatment with RP103, classified as mild renal failure. There was one patient (2%) with renal impairment during treatment with Cystagon.[6]

### Adherence to therapy

Eight patients were reported to have missed study doses during the trial, based on patient self-report or medication counts performed during clinic visits. This included five patients while taking RP103 and three patients while taking Cystagon. Three patients missed one or more consecutive days of study dosing (i.e., greater than four consecutive doses of Cystagon or greater than two consecutive doses of RP103). The remaining five patients missed less than one day of study dosing.[5]

### Swallowing

Swallowing difficulties were measured using a 10-point VAS, with 2-point increments in scoring from 0 (no pain) to 10 (very much pain). Eight of 39 patients (21%) reported a VAS score of greater than 4 at one time point during the study and 3/39 patients (8%) reported VAS scores of greater than 4 at more than one time point during the study. There were no statistical comparisons performed between groups. There were no clear differences in the reported degree of difficulty swallowing between the two treatment groups, but it did appear that the proportion of patients with VAS score greater than and equal to 2, was higher in both periods in both treatments, compared with the proportion with VAS score greater than and equal to 2 during the run-in period.[5] There were no data provided on swallowing scores prior to the run-in period, therefore it was not possible to compare pre-treatment and post-treatment swallowing scores. The minimal clinically important difference (MCID) is not known for this scale.

**Table 10: VAS Difficulty Swallowing Scores in Study RP103-03**

| VAS Difficulty Swallowing Score (0-10 scale)[a] | End of Run-In Period | Period 1 | | Period 2 | |
|---|---|---|---|---|---|
| | All Patients N = 39 | Cystagon N = 21 | RP103 N = 19 | Cystagon N = 21 | RP103 N = 20 |
| VAS Score = 0 | 30 (77) | 11 (52) | 13 (68) | 11 (52) | 12 (60) |
| VAS Score = 2 | 8 (21) | 9 (43) | 5 (26) | 5 (24) | 6 (30) |
| VAS Score = 4 | 1 (3) | 1 (5) | 1 (5) | 4 (19) | 1 (5) |
| VAS Score = 6 | 0 | 0 | 0 | 1 (5) | 0 |
| VAS Score = 8 | 0 | 0 | 0 | 0 | 1 (5) |
| VAS Score = 10 | 0 | 0 | 0 | 1(5) | 0 |

[a] Score represents the highest VAS score reported during the report period for each patient. Higher scores indicate more trouble swallowing.

N = total number of patients; VAS = visual analogue scale.

Source: FDA Medical Review.[5]

## Harms

Only those harms identified in the review protocol are reported below (Table 11).

### Adverse events

Adverse events that were reported after a dose of study drug or after day 1 of the study were as follows. Overall, 58% and 32% of patients reported adverse events during treatment with RP103 and Cystagon, respectively. Gastrointestinal adverse events were the most frequently reported category of adverse event and were reported in 14 patients (33%) during

treatment with RP103 and in nine patients (22%) during treatment with Cystagon. Of the more frequently reported adverse events, patients reported nausea (16%), vomiting (19%), and abdominal pain (9%) during treatment with RP103, compared with 7%, 12%, and 0% during treatment with Cystagon, respectively.[6]

The incidence of non-gastrointestinal adverse events in the study was 26% (11/43) during treatment with RP103 and was 10% (4/41) during treatment with Cystagon.

A subgroup analysis of the RP103-03 study was performed that hypothesized that RP103 would be associated with less severe halitosis due to dimethyl sulfide in the breath.[19] The authors showed non-statistically significant decreases in breath dimethyl sulfide during treatment with RP103, compared with breath levels taken during treatment with Cystagon (n = 4, *P* = 0.068 for Area Under the Curve of dimethyl sulfide levels). The authors did not measure the patients' personal experience of halitosis in this subgroup analysis.

### Serious adverse events

In the RP103-03 study, seven patients (16%) experienced a serious adverse event and six of these patients reported the SAE during treatment with RP103. SAEs reported during treatment with RP103 included abdominal discomfort, vomiting, hypokalemia, gastroenteritis, femur fracture, and knee deformity. One patient reported an SAE of hypovolemia during treatment with Cystagon (Table 11).

### Withdrawals due to adverse events

In the RP103-03 study, one patient experienced an adverse event leading to discontinuation. This was reported during treatment with RP103 and was related to mild cellulitis following an elective knee surgery (Table 11).

### Mortality

No patients died during the RP103-03 study.

## Table 11: Harms in Study RP103-03

| Parameter | Treatment Period | | | |
|---|---|---|---|---|
| | Run-In N = 43 | RP103 N = 43 | Cystagon N = 41 | Overall N = 43 |
| **Patients with ≥ 1 adverse event, n(%)** | **13 (30)** | **25 (58)** | **13 (32)** | **34 (79)** |
| Adverse events with overall incidence ≥ 5% | | | | |
| Vomiting | 3 (7) | 8 (19) | 5 (12) | 14 (33) |
| Nausea | 1 (2) | 7 (16) | 3 (7) | 10 (23) |
| Abdominal pain | 4 (9) | 4 (9) | 0 | 8 (19) |
| Headache | 2 (5) | 4 (9) | 0 | 5 (12) |
| Decreased appetite | 0 | 1 (2) | 2 (5) | 3 (7) |
| Hypokalemia | 0 | 3 (7) | 0 | 3 (7) |
| Cough | 1 (2) | 2 (5) | 0 | 3 (7) |
| Rhinorrhea | 3 (7) | 0 | 0 | 3 (7) |
| Renal impairment | 0 | 2 (5) | 1 (2) | 3 (7) |
| **Patients with ≥ 1 SAE, n(%)** | **0** | **6 (14)** | **1 (2)** | **7 (16)** |
| Abdominal discomfort | 0 | 1 (2) | 0 | 1 (2) |
| Vomiting | 0 | 1 (2) | 0 | 1 (2) |
| Hypokalemia | 0 | 1 (2) | 0 | 1 (2) |
| Hypovolemia | 0 | 0 | 1 (2) | 1 (2) |
| Gastroenteritis | 0 | 1 (2) | 0 | 1 (2) |
| Femur fracture | 0 | 1 (2) | 0 | 1 (2) |
| Knee deformity | 0 | 1 (2) | 0 | 1 (2) |
| **Patients with ≥ 1 AE leading to discontinuation, n(%)** | 0 | 1 (2) (*cellulitis*) | 0 | 1 (2) |

AE = adverse event; N = total number of patients; n = number of patients in subgroup; SAE = serious adverse event.

Source: Clinical Study Report.[6]

# Discussion

## Summary of Available Evidence

One pivotal trial evaluated the safety and efficacy of delayed-release cysteamine (RP103) to immediate-release cysteamine (Cystagon). The open-label crossover RP103-03 study enrolled patients with nephropathic cystinosis and all patients were treated with Cystagon during an open-label run-in period. The primary objective of the study was to test the noninferiority of the RP103 cysteamine formulation to Cystagon based on WBC cystine levels. Key limitations of the study included the small sample size, short duration of the study and the lack of blinding. Clinical outcomes that are of interest to patients were measured in this study, but the study was not designed to test differences between treatments for these outcomes.

## Interpretation of Results

### Efficacy

RP103 met the predefined criteria for noninferiority relative to Cystagon in a study that included patients who had been stabilized on Cystagon prior to randomization. The claim of noninferiority was based on WBC cystine level. WBC cystine is the only available biomarker for monitoring effectiveness of cystine-depleting treatment (see Appendix 4b). Newly diagnosed nephropathic cystinosis patients often have WBC cystine levels in the range of 3 to 10 nmol half cystine/mg protein, while controlled individuals generally have levels between 0.2 and 0.5 nmol half cystine/mg protein. In the RP103-03 study, the investigators selected a noninferiority margin of 0.3 nmol half cystine/mg protein. While the relationship between cystine levels and renal function has been described, the minimal clinically important change in WBC cystine has not been clearly established and therefore it is not known if the selected noninferiority margin is a good approximation of the minimal clinically important difference (Appendix 4b).

There were very few differences observed in the other outcomes measured in study RP103-03. There were very few statistical comparisons performed in this study for clinical outcomes. There were no large numerical differences in quality of life (PedsQL 4.0), adherence to therapy, or swallowing outcomes between the two cysteamine products. Data on survival and renal function were collected, but were uninformative because of the small size and short duration of the study.

There were several outcomes measured in the RP103-03 study that were also identified by patient groups as important, such as quality of life, survival, time to kidney transplant, or adherence to therapy. The study was very short and was not designed to test differences between the cysteamine products for these outcomes.

Drug levels were monitored during the RP103-03 study, and while pharmacokinetic parameters were not an outcome of interest in this review, research has shown that one hour after the ingestion of immediate-release cysteamine plasma levels of cysteamine reach a maximum, while WBC cystine levels drop to minimum levels.[20] This is followed by a gradual decline in cysteamine levels and a gradual increase in WBC cystine levels. Six hours after ingestion, both cysteamine and WBC cystine levels reach their original values. This has underscored the importance of adherence to this treatment every six hours, including the need for a nighttime dose to be administered.[20]

## Harms

The proportion of patients reporting adverse events in study RP103-03 was higher during treatment with RP103, compared with the period in which patients received Cystagon. The rates of gastrointestinal events were higher during treatment with RP103 (33%) than during treatment with Cystagon (22%). The investigators suggested that this may be explained by the lower usage of PPIs during treatment with RP103. This explanation may be valid and it illustrates the risk of gastrointestinal adverse events when RP103 is taken according to the product labelling.[15] The Canadian product monograph for Procysbi cautions against concomitant use of PPIs or other drugs that increase gastric pH because of variability with cysteamine absorption with Procysbi.

Non-gastrointestinal adverse events were also higher during treatment with RP103 (26%) compared with treatment with Cystagon (10%).

RP103-03 was a very short study. Signals of increase in harms were observed for gastrointestinal and non-gastrointestinal adverse effects. Relative risk of harm requires further study in future clinical trials. One open-label, non-comparative extension study (RP103-04) was conducted following the RP103-03 study. It included 40 patients from study RP103-03 and 19 additional patients, including 13 children under the age of seven and followed them for up to six months (Appendix 5). There is an open-label, non-comparative study (RP103-07) that has been completed and not yet published, but its preliminary findings were available. This study enrolled 41 patients, excluding patients less than 12 years of age (mean age 24.5 years), and followed them for up to 48 months. The non-comparative design and study withdrawal rates limit the extension studies' ability to provide new information regarding the relative efficacy and harms of Procysbi. The extension studies were able to demonstrate that treatment with RP103 over a longer time period can maintain WBC cystine within the target range (1 nmol half cystine/mg protein), however the non-comparative study failed to maintain a WBC cystine within this target range during RP103 treatment. Adverse events and serious adverse events were common and included diarrhea, vomiting, abdominal pain, and nausea.

## Other considerations

According to the clinical expert, cysteamine in the form of Cystagon is the most relevant comparator for Procysbi (RP103) in the Canadian context. Cystagon was available through Health Canada's Special Access Programme. Some provinces, such as Ontario, offer coverage to some patients. There is one other similar product available through the special access program, phosphocysteamine. Both immediate-release products became inaccessible during the course of the CDR review after Procysbi became available on the market in Canada.

## Potential place in therapy[1]

Currently nephropathic cystinosis is treated with a variety of supporting medications, but the disease-modifying agent is cysteamine. The agent is not marketed in Canada and is only available through special access request through Heath Canada. The clinical expert involved in the review stated that the administration of immediate-release cysteamine (either as phosphocysteamine or cysteamine) is fraught with several limitations: the medications

1 This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

require four-times-a-day strict dosing to enable stable levels leading to reduction of whole WBC cystine levels; the cysteamine metabolism is associated with higher peak levels, which is thought to contribute to the excretion of the drug into the skin and contribute to the sulphurous odour that impacts the social functioning of those affected; nonadherence to this medication occurs at a high frequency and is a considerable issue, not only due to the difficulty of administering a middle of the night dose, but because of the sulphurous odour in sweat and saliva; and 4) the prevalence of gastrointestinal side effects associated with this medication may limit achieving a therapeutic dose necessary to reduce whole WBC levels of cystine. Identification of a medication that allows for twice-daily administration with stable drug levels is expected to have beneficial effects on the side effect profile and adherence, and ultimately may facilitate easier attainment of reductions of whole WBC cystine levels to within therapeutic targets. The quality of life of the families caring for a patient with cystinosis is similarly likely to be positively impacted through improved sleep and simplification of the medical therapeutic regimen.

The clinical expert consulted for the review noted that, based on its design, included outcomes, and limited statistical comparisons, the RP103-03 study really only addresses the reduction of whole WBC cystine levels. The observed effect with Procysbi relative to Cystagon in the study likely indicates that Procysbi has a clinically meaningful effect in reducing cystine levels, similar to that of Cystagon; however, there remains uncertainty about the relative effects on other outcomes.

Nephropathic cystinosis patients are easily identified in Canada as there are at least two reference laboratories that are able to conduct the whole WBC cystine assay necessary for diagnosis.

## Conclusions

Results of a small crossover RCT indicated that Procysbi (RP103) is noninferior to Cystagon based on WBC cystine levels after three weeks of open-label treatment. A noninferiority boundary of 0.3 nmol half cystine/mg protein was selected but the minimal clinically important change in WBC cystine is not known. There were no clinically significant differences observed between the two cysteamine formulations for other outcomes such as adherence to therapy, swallowing ability, or quality of life, but the trial was not designed to show differences in these outcomes. The rates of serious adverse events, as well as non-serious gastrointestinal and non-gastrointestinal adverse events were higher during treatment with Procysbi compared with the rates observed during treatment with Cystagon.

# Appendix 1: Patient Input Summary

*This section was prepared by CADTH staff based on the input provided by patient groups.*

**1. Brief Description of Patient Group Supplying Input**

The Canadian Organization for Rare Disorders (CORD) is a registered charity that educates, advocates, and provides resources to patient groups of rare disorders. CORD advocates for health policy and a health care system that works for patients with rare disorders and their caregivers. CORD has received funding from Horizon in the past two years; however, CORD did not declare any conflict of interest with regard to this patient group submission.

**2. Condition-Related Information**

Information for the patient input submission was gathered using written individual testimonials or submissions, individual semi-structured interviews, and a survey created and administered by CORD. Individual interviews were performed to ascertain an in-depth understanding of cystinosis. The interview information was subsequently used to develop the survey. The survey was distributed through physicians, through one patient fundraising group using a snowballing technique, and through a posting on the Cystinosis Research Foundation (US) Facebook page. In addition, the survey was posted on Survey Monkey from June 30 to July 27, 2017 in English. Patients in Quebec were instructed to answer in either English or French, with responses subsequently translated. Five testimonials, six individual parent interviews (of children diagnosed with infantile cystinosis), and 71 survey responses (of which there was a mix of patients diagnosed with infantile, intermediate, or adult cystinosis, or who were parents/caregivers) were used to compose the submission. The average age of patients with cystinosis who were the patients of the interviews or survey responses was 15.1 years (range less than 1 year to 50 years of age), with all of the interview respondents living in Canada. Of the survey respondents, 62% were from Canada, 28% were from the US, and 5% where from elsewhere.

Patients with cystinosis experience a range of symptoms associated with the disease, including various gastrointestinal (GI) effects (e.g., vomiting, diarrhea, abdominal pain), muscle wasting, swallowing difficulties and gagging, halitosis, foul body odour, crystal buildup in the cornea/photosensitivity, extreme thirst and urination, reduced cognitive abilities, and rickets/softening of bones. Secondary impacts of the disease include kidney failure (which may occur in adolescence or early adulthood), multiple organ failure, and diabetes. With regard to patients with infantile cystinosis, parents often recollect that the first indications of the disease were vomiting, gagging, failure to thrive, and inability to roll over or lift the neck. Many parents were faced with multiple trips to the hospital emergency room and wrong diagnoses before finally obtaining the appropriate diagnosis, usually through a specialist.

The treatment regimen of Cystagon itself (which requires patients or caregivers to administer the medication every six hours) is very troublesome and burdensome. Patients and their caregivers continually have interrupted sleep which often negatively impacts all of the family members (not just caregivers and patients). In addition, patients and their families may experience reduced concentration and isolation (both social and emotional) due to the constant vigilance that is required for the care of cystinosis patients, in addition to regular clinic visits, trips to physiotherapists (to deal with weakened muscles and back pain), speech therapists, nutritionists, tutors, and psychotherapists. One caregiver described cystinosis as, "*Devastating – it has affected each and every one of us in his immediate and extended*

*family as well as personal friends, emotionally and financially and even socially."* Some parents have divorced due to the stress of the condition. Additionally, a number of parents discussed the tremendous financial burden of cystinosis, due to the direct cost of medications, supplements, and other supplies, non-reimbursed costs for health care visits, household expenses for modifications or other repairs, and the loss of income when parents have to provide continuous home care. As one parent stated, *"Despite the financial assistance we had with our benefits there were still a few years without coverage for the Cystagon and eye drops. That alone was equal to our mortgage and bills at the time. The travel, eating out, and parking costs. Increased water and hydro for the extra laundry... Replacing furniture and carpeting because of the many vomiting incidences. All the meds that were not covered. Diapers. Orthotics etc."*

As illustrated above, caring for a child or spouse with cystinosis and the treatment regimens that accompany it can be very challenging and burdensome. Caregivers of children with cystinosis are responsible for not only administering the treatment but also for taking care of the child, which often includes cleaning up after their many GI troubles, ensuring they eat well (which can be a daunting task in a child who has trouble swallowing), taking them to their various medical appointments, and taking care of their emotional needs (including those feelings of isolation experienced by children with cystinosis at school and socially). In those caregivers that have a spouse with cystinosis, there is often an increased burden on the caregiver, who may also have to take on the bulk of financial and family responsibilities. All of this leads to increased isolation, family and financial stress, and an increased burden on caregivers who may be limited or unable to work outside the home.

**3. Current Therapy-Related Information**

Of the 32 patients who responded to the medication portion of the survey, about 90% had received therapy, with 50% currently (and 36% in the past) receiving Cystagon as the main therapy. Of those Canadian respondents, 69% were currently on Cystagon while 15% had used it in the past. Respondents felt that Cystagon saves patients' lives, however it does not resolve all of the clinical problems of cystinosis (including deficits in sight, hearing, and cognition) and it is challenging to strictly adhere to the treatment regimen.

Noted side effects with Cystagon included mild to severe GI problems (nausea, vomiting, pain, and diarrhea), mild to very severe halitosis or skin odour, fever/chills, tiredness/dizziness, and decreased appetite. Many patients admitted to frequently not being able to follow the medication regimen of every six hours, although they were aware of the life-saving potential of Cystagon. Particular challenges reported with the medication included difficulty in taking the large number of capsules and in retaining the medication, the four times daily dosing, and the very bad taste and odour. Some parents would try to mask the taste in juice or food but then found it difficult to know how much medication their child was ingesting, especially with the associated gagging and vomiting that often ensued. Young children often used a gastrostomy feeding tube (G-tube) inserted into the stomach to avoid the problems of oral ingestion, which allow the caregiver to give the child the nighttime dose without having to awaken them. Older children however, often did not find the G-tube desirable and asked to have it removed.

The major consideration with regard to Cystagon is the four times daily administration. As one parent stated, *"Our lives are lived in 6-hour increments and governed by the strict adherence to a cycle of medication that keeps our child alive. Every aspect of our lives is impacted: sleep patterns, eating schedules, when we can/can't leave the house, how we plan and book holidays…"* Another consideration is the foul odour that accompanies using

Cystagon. As one parent stated, *"My daughter has been bullied, chastised, and discriminated against her entire life for the unescapable sulphur-like skin odour caused by the drug."*

Additional medications and supplements are also part of the treatment paradigm. Many patients take nutrient replacements (sodium, potassium citrate, phosphate, and vitamin D), medications to aid with stomach aches and heartburn, and anti-emetics. Some patients have also taken growth hormone therapy and hormone supplements. In terms of other treatments, some patients reported being on dialysis, and more than half of patient respondents claimed they had, or were indicated for, a kidney transplant.

**4. Expectations About the Drug Being Reviewed**

While almost all of the respondents were aware of Procysbi, most respondents understood the difference between Cystagon and Procysbi, with only 11% being unaware of the drug or how it differed.

The expectations associated with Procysbi centred on the twice-daily dosing schedule and the patients' hope for improved effectiveness and tolerability. The elimination of the nighttime administration was thought by many to mean that sleep would not be impacted. The elimination of the mid-day administration would help children to lead a more normal life. There was an expressed hope that cystine levels would remain low due to the extended-release form of Procysbi and that adverse events would be minimized. As one parent stated, *"It would mean my daughter and my husband and I could all sleep through the night. It would also mean that my daughter would not have to take it while at school. My hope is that her nausea will decrease to the point that she rarely vomits which will also in turn increase her appetite."*

In spite of the above comments, some patients and caregivers were hesitant about switching from Cystagon, mainly due to the lack of long-term experience or data associated with Procysbi. In addition, many respondents identified cost as a potential barrier to access as there is a difference in price. Procysbi may not be accessible, even to those who have insurance. As a result, many patients and caregivers still expressed a desire to have access to Cystagon.

Of the total respondents, 35% had experience with Procysbi; however, only 15% of the Canadian cohort had experience. Methods of receiving Procysbi differed, with 6% receiving it through a clinical trial, 24% receiving it through an expanded trial or compassionate access, and 59% (who were mostly from the US) as a drug plan benefit. No patients in Canada received Procysbi through their private insurance plan.

Almost all of the respondent expectations for Procysbi were positive, especially in terms of the twice-daily dosing schedule, potential for positive impact on quality of life, greater tolerability with fewer side effects, and hope for better long-term effectiveness on symptoms and disease progression. Some patients experienced immediate benefits, while others did not. Most patients and parents were aware that longer-term benefits would not be evident in the short-term. Side effects appeared to be minimized with Procysbi. As one patient stated, *"The side effects with Procysbi are…significantly less. The only downfall with Procysbi is the number of pills required since it only comes in 75 mg capsules."* Finally, most patients who had access to Procysbi felt that the benefits outweighed the risks and potentially unknown long-term effectiveness.

# Appendix 2: Literature Search Strategy

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | Embase 1974 to present<br>MEDLINE Daily and MEDLINE 1946 to present<br>MEDLINE In-Process & Other Non-Indexed Citations<br>**Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | September 6 2017 |
| Alerts: | Bi-weekly search updates until December 13 2017 |
| Study Types: | No search filters were applied |
| Limits: | No date or language limits were used<br>Conference abstracts were excluded |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| .sh | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| fs | Floating subheading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| # | Truncation symbol for one character |
| ? | Truncation symbol for one or no characters only |
| adj# | Adjacency within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .ot | Original title |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .kf | Author keyword heading word (MEDLINE) |
| .kw | Author keyword (Embase) |
| .pt | Publication type |
| .po | Population group [PsycInfo only] |
| .rn | CAS registry number |
| .nm | Name of substance word |
| pmez | Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present |
| oemezd | Ovid database code; Embase 1974 to present, updated daily |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| 1 | (Cysteamine bitartrate or Mercaptoethylamine hydrogen tartrate or Cystagon or EINECS 248-641-7 or Mercamine bitartrate or Mercaptoethylamine bitartrate or Procysbi or RP103 or RP 103 or QO84GZ3TST).ti,ab,kf,ot,hw,rn,nm. |
| 2 | 27761-19-9.rn,nm. |
| 3 | 1 or 2 |
| 4 | 3 use ppez |
| 5 | "Cysteamine"/ |
| 6 | (Becaptan or Aminoethanethiol or Aminoethylthiol or Mercaptoethylamine or CCRIS 3083 or Cisteamina or Cisteamina or Cystagon or Cystaran or Cysteamin or Cysteamine or Cysteinamine or Decarboxycysteine or EINECS 200-463-0 or HSDB 7353 or L 1573 or L1573 or Lambraten or Lambratene or MEA or Mercamine or Mercaptamina or Mercaptamine or Mercaptaminum or Mercaptoethylamine or NSC 647528 or NSC647528 or Riacon or Thioethanolamine or 5UX2SD1KE2 or WR 347 or WR347).ti,ab,kf,ot,hw,rn,nm. |
| 7 | 5 or 6 |
| 8 | 7 use ppez |
| 9 | "Delayed-Action Preparations"/ |
| 10 | (Modified release or extended release or sustained release or slow release or controlled release or delayed release or prolonged release or time release or timed release or sustained action or delayed action or prolonged action or long action or long acting or longacting or longer acting or extended duration or long duration or longer duration or prolonged duration or once daily or one a day or duration of action or controlled drug release or transdermal or OROS or osmotic release or osmotic delivery or controlled delivery).ti,ab,kf. |
| 11 | 9 or 10 |
| 12 | 11 use ppez |
| 13 | exp Cystinosis/ |
| 14 | ((renal or kidney* or nephropath*) adj3 cystinosis).ti,ab,kf. |
| 15 | (defect adj2 (cysteine or CTNS or Cystinosin)).ti,ab,kf. |
| 16 | (cholesterol adj2 ester adj2 stor* adj2 (disorder* or diseas* or defect*)).ti,ab,kf. |
| 17 | ((abderhalden or fanconi or cystine storage) adj2 (disease or syndrome)).ti,ab,kf. |
| 18 | or/13-17 |
| 19 | 18 use ppez |
| 20 | 8 and 12 |
| 21 | 8 and 19 |
| 22 | 4 or 20 or 21 |
| 23 | (Cysteamine bitartrate or Mercaptoethylamine hydrogen tartrate or Cystagon or EINECS 248-641-7 or Mercamine bitartrate or Mercaptoethylamine bitartrate or Procysbi or RP103 or RP 103 or QO84GZ3TST).ti,ab,kw. |
| 24 | 23 use oemezd |
| 25 | *mercaptamine/ |
| 26 | (Becaptan or Aminoethanethiol or Aminoethylthiol or Mercaptoethylamine or CCRIS 3083 or Cisteamina or Cisteamina or cystadrops or Cystagon or Cystaran or Cysteamin or Cysteamine or Cysteinamine or Decarboxycysteine or dropcys or EINECS 200-463-0 or HSDB 7353 or L 1573 or L1573 or Lambraten or Lambratene or MEA or Mercamine or Mercaptamina or Mercaptamine or Mercaptaminum or mercaptoamine or mercaptoethanolamine or Mercaptoethylamine or nsc 25116 or nsc25116 or NSC 647528 or NSC647528 or Riacon or Thioethanolamine or 5UX2SD1KE2 or WR 347 or WR347).ti,ab,kw. |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **Line #** | **Search Strategy** |
| 27 | 25 or 26 |
| 28 | 27 use oemezd |
| 29 | *delayed release formulation/ |
| 30 | (Modified release or extended release or sustained release or slow release or controlled release or delayed release or prolonged release or time release or timed release or sustained action or delayed action or prolonged action or long action or long acting or longacting or longer acting or extended duration or long duration or longer duration or prolonged duration or once daily or one a day or duration of action or controlled drug release or transdermal or OROS or osmotic release or osmotic delivery or controlled delivery).ti,ab,kw. |
| 31 | 29 or 30 |
| 32 | 31 use oemezd |
| 33 | exp Cystinosis/ |
| 34 | ((renal or kidney* or nephropath*) adj3 cystinosis).ti,ab,kw. |
| 35 | (defect adj2 (cysteine or CTNS or Cystinosin)).ti,ab,kw. |
| 36 | (cholesterol adj2 ester adj2 stor* adj2 (disorder* or diseas* or defect*)).ti,ab,kw. |
| 37 | ((abderhalden or fanconi or cystine storage) adj2 (disease or syndrome)).ti,ab,kw. |
| 38 | or/33-37 |
| 39 | 38 use oemezd |
| 40 | 28 and 32 |
| 41 | 28 and 39 |
| 42 | 24 or 40 or 41 |
| 43 | conference abstract.pt. |
| 44 | 42 not 43 |
| 45 | 22 or 44 |
| 46 | remove duplicates from 45 |

| OTHER DATABASES | | |
|---|---|---|
| PubMed | A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used. | |
| Trial registries (Clinicaltrials.gov and others) | Same keywords, limits used as per MEDLINEdline search. | |

## Grey Literature

| | |
|---|---|
| Dates for Search: | September 2017 |
| Keywords: | Procysbi, Cystinosis |
| Limits: | No date or language limits used |

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

# Appendix 3: Excluded Studies

| Reference | Reason for Exclusion |
|---|---|
| Dohil et al.[21]<br>Langman et al.[22]<br>Manz et al.[23]<br>Nesterova et al.[24]<br>Medic et al.[25]<br>Ahlenstiel-Grunow et al.[26]<br>Prescrire 1999[27]<br>Greco et al.[28]<br>Gahl et al.[29]<br>Cochat et al.[30] | Inappropriate study design |
| Devereux et al.[31] | Different indication |
| Gahl et al.[32]<br>Gahl et al.[33]<br>Tsilou et al.[34] | Inappropriate intervention |
| Langman et al.[35]<br>Bertholet-Thomas et al.[36]<br>Van Stralen et al.[37] | No comparator |

# Appendix 4: Validity of Outcome Measures

## Aim

To summarize the validity of the following outcome measures:

- Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL 4.0)
- Short Form 36 (SF-36)
- Visual analogue scale (VAS) for swallowing

## Findings

### Pediatric Quality of Life Inventory Version 4.0 Generic Core Scales (PedsQL 4.0)

The original Pediatric Quality of Life Inventory (PedsQL) was developed as a health-related quality of life (HRQoL) measure that addressed the paucity of appropriately validated and reliable instruments incorporating both the child and parental experience with chronic health conditions. The PedsQL uses a modular approach and incorporates both generic and disease/symptom specific items that are appropriate for the assessment of pediatric chronic conditions.[38] The generic HRQoL measure was developed using pediatric cancer as the model, due to the fact that consequences of pediatric cancer (rather than specific cancer symptoms) are applicable to many other pediatric chronic health conditions.[38] The PedsQL 4.0 Generic Core Scales comprise 23 items under the following modules: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items).[39] These Generic Core Scales are comprised of both the parent proxy report and the child self-report formats that assess health perceptions. The child self-report format is specific for ages 5 years to 7 years, 8 years to 12 years, and 13 years to 18 years of age, while the corresponding parent proxy reports are specific for toddlers (ages 2 years to 4 years, for which there is no child self-assessment report), young children (ages 5 years to 7 years), children (ages 8 years to 12 years), and adolescents (ages 13 years to 18 years). The questions ask how much of a problem each item has been in the past month. A 5-point Likert response scale is used across the child reports (from ages 8 years to 18 years) and the corresponding parent report, and include the following responses with corresponding scores: 0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; and 4 = almost always a problem. In addition, a 3-point scale is used for simplification and ease of use for children who are aged 5 years to 7 years and include 0 = not at all a problem; 2 = sometimes a problem; and 4 = a lot of a problem, with each of the response choices anchored to a happy face to sad face scale.[39] The scores, which are reversed scored, are transformed linearly to a 0 to 100 scale, whereby 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0, with higher scores indicative of a higher HRQoL. In order to account for missing data, the sum of the items divided by the number of items that are answered is computed in order to ascertain the scale score. If greater than 50% of the items within the scale are missing, then the scale score cannot be obtained. In order to ascertain the Psychosocial Health Summary Score (comprised of 15 items), the sum of the items is divided by the items answered in the School Functioning, Emotional, and Social Subscales.[39] There are currently more than 60 translations of the PedsQL 4.0 that have been validated.[40,41]

In order to validate the PedsQL 4.0, a sample of chronically ill (as reported by their parents in a specialty clinic [n = 683]), acutely ill (parents reported no presence of chronic illness and attended a specialty clinic [n = 207]), and healthy children (identified at their physician's office during regular visits or using telephone calls [n = 730]) between the ages of two years to 18 years were included.[39] Construct validity was ascertained using the known-groups method, whereby scale scores were compared across groups that are known to differ in the specific health constructs being examined (in this case healthy versus acute or healthy versus chronic conditions). In addition, potentially confounding factors such as age, gender, and ethnicity were also examined across health states. Hypothesizing that healthy children would have a higher HRQoL, Varni et al. noted that the PedsQL 4.0 differentiated between the different health states (healthy, acute, and chronically ill) and it also correlated with illness burden and morbidity measures.[39] Internal consistency reliabilities generally exceeded the standard alpha coefficients of 0.70. The total scale scores across the ages for the self-report and proxy-report were 0.88 and 0.90, respectively, thus indicating this as an appropriate primary analysis summary score. The Physical Health and Psychosocial Health Summary Scores were greater than 0.8 for the self-report and the proxy-report; hence, the authors determined they were best for secondary analyses. The Emotional, Social, and School Functioning Subscales generally obtained alpha coefficients around 0.70; therefore, the authors suggested these be used for descriptive or exploratory analyses.[39]

Varni et al.[42] then examined three studies in order to determine the sensitivity and responsiveness of the PedsQL 4.0 Generic Core Scales. The population included pediatric patients (age range 2 years to 18 years) with acute or chronic health conditions (n = 115 presenting to a cardiology clinic; n = 47 presenting to an orthopedic clinic; n = 127 presenting to a rheumatology clinic) and their parents. Statistically significant differences were observed between pediatric patients defined as New York Health Assessment (NYHA) Class II/IV and Classes I and II, suggesting that the PedsQL 4.0 was likely to be sensitive.[42] Likewise, statistically significant changes between the initial and follow-up visit of patients attending the orthopedic clinic were observed (and the follow-up visit results also corresponded to that of healthy children responses), demonstrating the responsiveness of the PedsQL 4.0.[42] In another study by Desai et al.,[43] patients admitted to medical or surgical units were administered the PedsQL 4.0 upon admission (64.5%; n = 4,637/7,184) and during follow-up (58.1%; n = 2,694/4,637). The responsiveness of the PedsQL 4.0 was demonstrated upon examination of the mean differences between admission and follow-up; 22.1 (standard deviation [SD] of 22.7) for the total score, 29.3 (SD of 32.4) for the physical domain, and 17.1 (SD of 21.0) for the psychosocial domain. Moderate variability in responsiveness was observed by age and minimal variability in responsiveness was observed for patients having been admitted for medical or surgical reasons.[43] Construct validity was further demonstrated as patients with no chronic illness (and their parents) scored higher on the total score, physical domain, and psychosocial domain when compared with patients with either complex or non-complex chronic illness.[43]

No minimal clinically important difference (MCID) has been identified for any specific chronic or acute condition, including nephropathic cystinosis.

### Short Form 36 (SF-36)

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[44] The SF-36 consists of eight health domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH).[44-46] For each of the

eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status.[44,45] The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and an SD of 10 in the general US population. Therefore, all scores above/below 50 are considered above/below average for the general US population. The SF-36 has been validated in a variety of disease conditions.[46-48]

On any of the scales, an increase in score indicates improvement in health status. In general use, a change of 2 points in the SF-36 PCS and 3 points in the SF-36 MCS indicates a clinically meaningful improvement as determined by the patient.[49] Based on anchor data, the SF-36 User's Manual also proposed the following minimal mean group differences, in terms of t score points, for SF-36v2 individual dimension scores: PF, 3; RP, 3; BP, 3; GH, 2; VT, 2; SF, 3; RE, 4; and MH, 3. It should be noted that these minimally important difference (MID) values were determined as appropriate for groups with mean t score ranges of 30 to 40. For higher t score ranges, MID values may be higher.[49] No MCID values were identified that were specific to patients with nephropathic cystinosis.

Two versions of the SF-36 exist: the original and the SF-36 version 2 (SF-36v2 was made available in 1996).[49] The SF-36v2 contains minor changes to the original survey, including changes to: instructions (reduced ambiguity), questions and answers (better layout), item-level response choices (increased), cultural/language comparability (increased), and elimination of a response option from the items in the mental health and vitality dimensions.[49]

### Visual Analogue Scale (VAS) for Swallowing

The manufacturer used a VAS for swallowing scale in order to assess the pain a patient with nephropathic cystinosis may experience when swallowing.[18] This VAS scale contained a 0 to 10 metric with 0 = no pain with swallowing and 10 = very much pain with swallowing. No additional evidence was identified in a supplemental search with regard to the validity or reliability of this outcome measure in any type of patient. In addition, no MCID was identified in any type of patient.

## Table 12: Validity of Outcomes

| Instrument | Type | Evidence of Validity | MCID | References |
|---|---|---|---|---|
| PedsQL 4.0 Generic Core Scales | • Patient-report and parent-report (specific for different ages)<br>• 5-point Likert scale for patients ≥ 5 years of age<br>• 3-point Likert scale for patients < 5 years of age, anchored to happy to sad faces | YES | UNKNOWN | Varni et al. 1999[38]<br>Varni et al. 2001[39]<br>Varni et al. 2002[42] |
| SF-36v2 | Generic tool to measure multidimensional health concepts and capture a full range of health states | YES | General (non-disease specific) MID: 2 points in PCS; 3 points in MCS; 2 to 4 points for individual dimensions<br><br>None for patients with nephropathic cystinosis | SF-36v2 User's manual[49] |
| VAS for swallowing | VAS scale: 0 to 10 metric, where 0 = no pain with swallowing and 10 = very much pain with swallowing | NO | UNKNOWN | CSR RP103-03[18] |

CSR = Clinical Study Report; MCID = minimal clinically important difference; MCS = Mental Component Summary; MID = minimal important difference; PCS = Physical Component Summary; PedsQL 4.0 = Pediatric Quality of Life Inventory version 4.0; SF-36v2 = Short Form 36 Health Survey version 2; VAS = visual analogue scale.

## Conclusion

The PedsQL 4.0 Generic Core Scales are a validated and reliable patient and parent measure that accurately reflect the burden of disease in chronically and acutely ill children. There is no MCID that has been identified for any specific chronic condition, including patients who have nephropathic cystinosis.

The SF-36 was developed as a generic HRQoL measure and has shown good validity and reliability in many populations; however, the performance of each dimension and of the summary component scores varies between populations and according to study design. No specific evidence was identified with regard to the validity or reliability of the SF-36 in patients with nephropathic cystinosis. In addition, no MCID has been established in this population.

The VAS for swallowing that the manufacturer used to assess pain while swallowing has not been validated or deemed a reliable measure in any type of patient. In addition, no MCID has been established in any population of patients.

# Appendix 4b: Validity of Outcome Measures

## Aim

To summarize the following outcome measures:

- White blood cell (WBC) cystine levels.

## Findings

An increased WBC cystine level is currently considered to be the gold standard for diagnosing suspected cases of nephropathic cystinosis.[1,3,50] WBC cystine level remains the only available biomarker for monitoring the effectiveness of cystine-depleting treatment, as well as treatment adherence.[1,3,50]

One hour after the ingestion of immediate-release cysteamine, plasma levels of cysteamine reach a maximum while WBC cystine levels drop to minimum levels.[20] This is followed by a gradual decline in cysteamine levels and a gradual increase in WBC cystine levels. Six hours after ingestion, both cysteamine and WBC cystine levels reach their original values. This has underscored the importance of adherence to this treatment every six hours, including the need for a nighttime dose to be administered.[20]

High-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) is generally the assay method for measuring WBC cystine levels. It can be performed within 20 minutes and is fully automated.[3]

### Reference Range

Newly diagnosed nephropathic cystinosis patients are found to have WBC cystine levels in the range of 3 to 10 nmol half cystine/mg protein, while control individuals and heterozygous carriers generally have levels between 0.2 and 0.5 nmol half cystine/mg protein, respectively.[1,4,50,51] While on cystine-depleting treatment, patients targeting “good therapeutic control” should be maintained under a threshold level of 1 nmol half cystine/mg protein to delay disease progression.[1,3,50]

### Correlation with Clinical Outcomes and Minimally Important Clinical Difference

The WBC cystine levels at which progressive renal failure and extrarenal complications can be prevented is unknown. Therefore, the 90$^{th}$ percentile of cystine levels in polymorphonuclear cells (less than 1 nmol half cystine/mg protein) found in asymptomatic heterozygotes has historically been used as the upper WBC cystine limit when monitoring therapy.[3]

Two retrospective studies have examined the relationship between depletion of WBC cystine levels and renal disease in nephropathic cystinosis patients at the point of diagnosis up until renal failure or transplantation.[24,52] Both studies examined peak WBC cystine levels recorded throughout treatment, within similar stratifications (less than 1.0, 1.0 to 2.0, and greater than 2.0 nmol half cysteine/mg protein) as well as the rate of deterioration in renal function. In one study,[24] a mean WBC cystine level was derived from all readings between the patient’s first visit to the time of renal failure, with an average of 35 ± 3 readings per patient. A composite score involving extent of WBC cystine depletion and duration was

calculated for each patient.[24] Age at renal failure was found to vary inversely with mean WBC value, with a large scatter, and it was estimated that for every 1 nmol half cystine/mg protein increase in mean WBC cystine value, approximately nine months of renal function was lost.[24] There was a direct relationship found between consistently low levels of WBC cystine (less than 1 nmol half cystine/mg protein), preservation of remaining renal glomerular function, and increased age of end-stage renal disease (ESRD) ($R^2 = 0.61$).[24] Similar results were found with the second study,[52] which also evaluated WBC cystine and renal function in cystinosis patients treated with cystine-depleting therapy. For this study, a parameter for rate of renal deterioration was used, based upon the linear relationship between reciprocal serum creatinine and age.[52] In patients where median WBC cystine was less than 1 nmol half cystine/mg protein, a lower parameter value of renal deterioration was found than in those with a median WBC cystine value between 1 and 2 nmol half cystine/mg protein ($P = 0.064$), and those noncompliant with treatment ($P = 0.006$).[52] Although in both studies renal damage associated with cystinosis was considered to be irreversible, consistently low WBC cystine levels were found to be inversely related to the degree of existing renal damage.[24,52]

One prospective study[53] evaluated the white matter integrity in 48 children between the ages of three years and seven years with a mean age of 5.5 ± 1.3 years. Half of these children were diagnosed with infantile nephropathic cystinosis with no known history of pulmonary dysfunction or diabetes mellitus, and the remaining half were healthy children. A positive correlation was found between white matter alterations and elevated WBC cystine levels in children greater than five years of age, indicating that there may be an early delay in white matter maturation in children with consistently high WBC cystine levels. Furthermore, there was a signal that increased WBC cystine may have an influence on white matter organization and connectivity, resulting in persistent cognitive skill deficits.[53]

## Reliability

HPLC-MS/MS is known to have a low detection limit of WBC cystine concentrations.[54] The standard deviation range with this technique is small (less than 15% root mean square error), which reflects the reliability of this method for determining intracellular levels of cystine.[54]

The main variability in the assay lies in the method of WBC separation, therefore separation methods should be carried out soon after blood draw, and techniques must be standardized for each laboratory. Shipping of whole blood samples is not advisable due to increases in intracellular cystine content when samples are left at room temperature for 24 hours.[3,55] The clinical expert involved in the CDR review noted that there are currently few laboratories in Canada set up to analyze WBC cystine levels; the laboratory at Montreal Children's Hospital uses the assay to analyze samples and Calgary is setting up another reference laboratory. The expert stated that samples must remain on ice prior to testing, and that specific protocols must be followed; therefore, errors may occur leading to inaccurate analyses.

There is also documentation to show variability in the types of cells used in the assay, as there is a preferential accumulation of cystine found in polymorphonuclear leukocytes (PMN) and monocytes.[55] When using a traditional mixed WBC sample, there is an unpredictable risk of a falsely low reading of cystine levels if there is a high proportion of lymphocytes in the sample.[3,4,51] An assay using immunopurified PMN leukocytes has been demonstrated to be a more sensitive method of measuring WBC cystine levels. One study examined 26 blood samples of nephropathic cystinosis patients split into duplicates and prepared both by mixed WBC method and PMN leukocyte method.[51] The values of cystine/protein measured

in the PMN leukocyte sample were found to be higher than the values in the mixed WBC sample (1.9 versus 1.0 nmol half cystine/mg protein, $P < 0.001$).[51] Due to the risk of a falsely low reading with a mixed WBC sample, a PMN leukocyte assay has been recommended to be used instead whenever possible.[3,4,51,55]

## Conclusion

Due to the rare, multi-faceted nature of nephropathic cystinosis, outcome measurements can be difficult to assess over time, and a large emphasis has been placed on using WBC cystine values as a means to diagnose as well as guide therapy. This test has been specifically designed to reflect the pathogenesis of this disease, and is replicable in a laboratory setting.[3,55] The reference values for this test were initially based on the 90th percentile WBC cystine value found in heterozygous individuals who are asymptomatic.[3] The relationship between WBC levels and rate of disease progression has been reinforced in a few retrospective studies.[24,52]

# Appendix 5: Summary of Studies Without Control Groups

## Aim

To summarize the details and findings of the ongoing RP103-03 extension study, RP103-04[56] and an ongoing open-label study, RP103-07.[17]

## Findings

### Study Design

*RP103-04*

This extension study was an open-label, single-arm trial designed to evaluate the efficacy, safety, and tolerability of delayed-release cysteamine in adult and pediatric patients with cystinosis. Secondary objectives assessed long-term quality of life and pharmacokinetics. The study design, populations, treatments, and outcomes are summarized in Table 13.

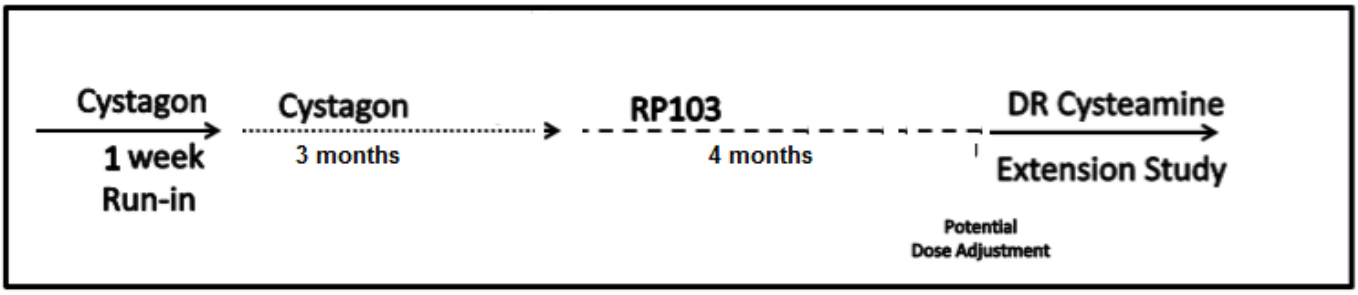
Patients who had completed study RP103-03 were eligible for RP103-04. These patients were required to complete a minimum of six consecutive monthly visits followed by quarterly visits throughout their participation in the study. New patients (≤ 6 years of age, or had received a kidney transplant; both had to have previously been on a stable dose of Cystagon for at least 21 days) could also be enrolled if they attended a screening visit within 28 days prior to day 1 of the study, followed by a dose confirmation period for five days, in accordance with plasma cysteamine and WBC cystine levels.

*RP103-07*

This phase IIIb study was an open-label, single-arm, switch trial designed to test safety, tolerability and effectiveness of RP103 following switch from Cystagon in pediatric and adult patients (≥ 12 years of age) with nephropathic cystinosis in the US and European Union. The primary objective of the study was to compare Cystagon and RP103 at steady state WBC cystine levels evaluated after three months and to assess the long-term safety and tolerability of RP103 in patients with cystinosis.[17,57]

The study consisted of a one week screening period, followed by a three-month Cystagon treatment phase, followed immediately by a four-month RP103 treatment phase (Figure 3). Thereafter, patients who had completed the total seven-month treatment phase could continue to receive RP103 in the long-term phase of the study.[17,57]

## Figure 3: Study Design of RP103-07




DR = delayed-release.
Source: Clinical Summary[17]

### Population Demographics and Baseline Disease Characteristics

*RP103-04*

Demographic and baseline disease characteristics for RP103-treated patients who participated in study RP103-04 are described in Table 14.

A total of 60 patients were enrolled in RP103-04, 40 of whom participated in study RP103-03, and 20 of whom were newly enrolled. Of the 20 newly enrolled patients, 14 were less than or equal to six years of age and six had previously undergone renal transplantation. The overall mean age at start of treatment was 10.9 years (range 2 years to 32 years) and 61.7% were male.[17,56]

*RP103-07*

The population characteristics for this study are summarized in Table 15. The study recruited 41 patients older than the age of 12 years, with a mean age of 24.5 years, and 48.8% of patients were male.[57]

### Intervention

*RP103-04*

Patients who had completed study RP 103-03 continued to receive open-label RP103 at the same dose every 12 hours in study RP103-04 from the time of the last dose prescribed in RP103-03. These patients were then required to complete a minimum of six consecutive monthly visits in RP103-04, followed by quarterly visits thereafter, throughout their participation in the study.[17,56]

Patients who were newly enrolled attended a screening visit within 28 days prior to day 1 of the study, followed by a dose confirmation period, which took place from day 1 to day 5 of the study, and during which trough cysteamine and peak WBC cystine levels were drawn. The day 1 visit was performed in the morning under fasting conditions, where patients received their first dose of RP103 every 12 hours, at a starting dose equal to 70% of the total daily Cystagon dose at the day of screening. Thereafter, patients attended quarterly follow-up visits throughout their participation in the study.[17,56]

The investigator was responsible for reviewing plasma cysteamine and WBC cystine levels and safety data prior to scheduled visits to determine any need for dose adjustment for RP103. Patients who did not achieve a target WBC cystine of less than and equal to 1 nmol half cystine/mg protein, or who did not tolerate their dose as determined by the investigator, were to have their RP103 dose adjusted or be terminated from the study.[56]

*RP103-07*

All patients participating in RP103-07 completed a seven-day screening period leading up to day 1, when study eligibility was established and patients continued to be treated with Cystagon. On day 1, eligible patients were enrolled and received a randomized assignment to non-morning collection time points for study visits during the Cystagon treatment phase in the first three months.[17,57]

During the three-month Cystagon treatment phase, patients were treated with their usual dose of Cystagon for three months with no dose adjustments. During the subsequent four months, patients were treated with RP103 every 12 hours, starting at a total daily dose of 70% of their Cystagon dose, with dose increases permitted only during the first month of dosing with RP103 (i.e., at month 3.5 or month 4 visits). During the seven-month treatment phase, study visits occurred monthly during both the three-month Cystagon treatment phase and the four-month RP103 treatment phase, with one additional study visit at month 3.5 to assess WBC cystine levels for potential dose increases during the first month of RP103 treatment. Dose adjustments of RP103 were not permitted during months 5, 6, and 7 of the RP103 phase.[57]

Patients completing the initial seven-month treatment phase were able to continue to participate in the long-term phase and receive RP103 until it became available through market approval in their region, until treatment duration achieved a maximum of 48 months, or the patient withdrew from the study.[57] During the long-term phase of the study, patients were to attend study centre visits on a quarterly basis for the remainder of their participation. During this period, samples were only collected after the morning dose, and central WBC cystine results were unblinded to study investigators for dose adjustments to be made.[57]

## Outcomes

### *RP103-04*

The primary efficacy outcomes measured in this extension period were a WBC cystine concentration measured 30 minutes post-dose at each study visit, and the dose of RP103 which was summarized descriptively and as a proportion of their baseline Cystagon daily dose. These outcomes were obtained at monthly intervals for the first six months and then quarterly.[56]

Other outcomes reported in the study were quality of life, which was measured via Pediatric Quality of Life Inventory (PedsQL 4.0) (for patients less than 19 years of age) or the Short Form 36 (SF-36) (for patients greater than and equal to 19 years of age), renal function (assessed via estimated glomerular filtration rate [eGFR]), growth (assessed via height Z-scores for age and gender from Centers for Disease Control and Prevention [CDC] growth charts) and swallowing difficulty (assessed via visual analogue scale [VAS]) recorded at study visits.[56]

### *RP103-07*

The main efficacy outcome for this study was to compare WBC cystine levels at steady state between Cystagon and RP103 after three months of each treatment. The main safety outcome for this study was to examine the adverse events and serious adverse events found to be associated with RP103 treatment.[57]

To measure WBC cystine control over 24 hours, blood samples were collected twice at each visit: 15 minutes before the morning dose and within 15 minutes before the non-morning dose which was randomized to them. During the first month of RP103 treatment, samples were collected only once per visit, 30 minutes after each morning and evening dose. Investigators were blinded to the central laboratory WBC cystine results during the initial 7-month treatment phase. Dose increases were permitted based on WBC cystine levels during the first month on RP103 only upon written notification by the sponsor medical officer for safety considerations.[57]

Secondary outcomes were to examine differences in patient quality of life between the use of Cystagon and RP103 via the SF-36 and PedsQL questionnaires, and to evaluate changes in swallowing assessments carried out via VAS. Blood sample measurements were also collected 15 minutes before the dose of Cystagon and 30 minutes after the dose of RP103 at each visit. Pharmacodynamic measurements compared the rate of WBC cystine levels on day 7 of the treatment period for Cystagon and day 7 of the treatment period for RP103.[17,57]

## Patient disposition and exposure

### *RP103-04*

RP103-03 randomized 43 patients, of whom 40 progressed to the extension study up to completion. An additional 20 patients were recruited from two different subgroups: 14 patients less than and equal to 6 years old and six patients who had previous kidney transplant.[17] Of the additional 20 patients recruited, one patient in the less than and equal to 6 years old subgroup did not receive at least one dose of RP103, and this patient was therefore not included in the final analysis.[17] The median exposure time for all included

patients was 3.0 years (1,100 days, range 35 days to 1,677 days). Patient exposure in this study is summarized in Table 16.[56]

For 19% of patients (11/59), their duration of exposure to RP103 was under 24 months. The majority of patients were in the trial for longer than 24 months (81%, 48/59) and 46% (27/59) stayed in the trial for longer than 36 months. For nine patients, the duration of exposure was greater than 48 months.[56]

The disposition of patients in this study is summarized in Table 16. As of the interim data cut-off on March 31, 2015, 29 patients were continuing in the study, 25 patients exited the study to transition on to the commercially-available drug (Procysbi), and six patients discontinued from the study for other reasons (three patients discontinued due to adverse effects, one patient withdrew consent, and one patient discontinued due to a physician decision). As a result, a total of 59 patients received the study drug and had pharmacokinetic/pharmacodynamic measurements included for analysis.[56]

*RP103-07*

For this trial, 43 patients were screened and signed for consent, after which 41 were enrolled to receive the study drug during the initial three-month Cystagon treatment phase and during the subsequent 4-month RP103 treatment phase. All 41 patients who were enrolled completed two phases of the study, although there was missing data for one of these patients with respect to the primary outcome.[57] Based on interim data (collected April 10, 2015), two patients withdrew during the long-term phase, 11 patients completed the study during the long-term phase (remained in the study for at least 24 months), and 28 patients were ongoing in the long-term phase of the study. One patient withdrawal in the long-term phase was elective and the second patient withdrawal was due to a protocol violation.[57] Patient disposition is further summarized in Table 17.

## Table 13: Details of Additional Studies

| | | RP103-04 | RP103-07 |
|---|---|---|---|
| Designs & Populations | **Study Design** | Phase III, multi-centre, multi-national, open-label, extension | Phase IIIb, international multi-centre, open-label, uncontrolled study |
| | **Locations** | 10 sites in the US, France, Netherlands | US, Belgium, France, Italy, Netherlands, UK |
| | **Number of Participants (N)** | 60 | 41 |
| | **Inclusion Criteria** | Pts previously participating in RP103-03 and willing to continue with treatment<br>OR<br>Pts with:<br>• confirmed diagnosis of nephropathic cystinosis;<br>• stable on a Cystagon dose at least 21 days prior to screening;<br>• no significant changes in liver function tests and renal function 6 mos before screening;<br>• eGFR > 30 mL/min/1.73m$^2$;<br>• female pts of childbearing potential who agree to use contraception. | • Confirmed diagnosis of nephropathic cystinosis<br>• On a stable dose of Cystagon at least 21 days prior to screening<br>• WBC cystine level > 1 nmol half cystine/mg protein over at least 2 measurements in the 2 yrs prior to screening<br>• eGFR > 20 mL/min/1.73m$^2$ and no significant change in renal function within 6 mos before screening |
| | **Exclusion Criteria** | Pts enrolled in RP103-03 who did not complete last scheduled study visit or did not wish to continue treatment with RP103<br>OR, for pts who did not complete RP103-03: | Pts < 12 yrs of age.<br>Pts with current history of any of the following conditions:<br>• inflammatory bowel disease, or prior resection of |

| | | RP103-04 | RP103-07 |
|---|---|---|---|
| | | • Pts less than 1 year old.<br>• Pts with known history currently of the following conditions or other health issues that, in the opinion of the investigator, make it unsafe for participation:<br>○ inflammatory bowel disease (if currently active) or prior resection of small intestine;<br>○ heart disease (i.e., myocardial infarction, heart failure, unstable arrhythmias, or poorly controlled hypertension) 90 days prior to screening;<br>○ active bleeding disorder 90 days prior to screening;<br>○ malignant disease within last 2 yrs.<br>• Pts with hemoglobin level < 10 g/dL at screening or a level that, in the opinion of the investigator, makes it unsafe for participation.<br>• Pts with known hypersensitivity to cysteamine or penicillamine.<br>• Female pts who are nursing, planning a pregnancy, known or suspected to be pregnant, or have a positive serum pregnancy test.<br>• Pts who, in the opinion of the investigator, are unable or unwilling to comply with the protocol. | the small intestine;<br>• heart disease (i.e., myocardial infarction, heart failure, unstable arrhythmias, or poorly controlled hypertension) within 90 days prior to screening;<br>• active bleeding disorder within 90 days prior to screening;<br>• history of malignant disease within 2 yrs prior to screening. |
| | **Objective** | To evaluate long-term efficacy, safety, and PK of delayed-release cysteamine bitartrate (after 9-wk initial study, RP103-03) | Primary: Compare initial Cystagon phase and subsequent RP103 phase in pts to evaluate control of WBC cystine levels over 24 hours.<br>Secondary: Assess long-term safety and tolerability of RP103 in pts with cystinosis. |
| EXPOSURE | **Intervention** | Long-term treatment of RP103 q.12.h. starting at a total daily dose of 70% of participants' total daily Cystagon dose, with opportunity for quarterly dose adjustments. | RP103 q.12.h. from mos 3.5, 4, 5, 6, and 7, starting at a total daily dose of 70% of participants' total daily Cystagon dose with no dose adjustments<br>Long-term treatment: RP103 q.12.h. with opportunity for quarterly dose adjustments |
| | **Phase** | III | IIIb |
| | Extension Period | 9 wks + 1 dose up to a minimum of 6 mos (median exposure 3.0 yrs, range of 35 to 1,677 days) | Mos 8 to 48, or study termination |
| | Follow-up | 6 mos after study completion | 7 ± 2 days after last study dose or decision to terminate |
| OUTCOMES | **Main End Point(s)** | Mean WBC cystine content<br>Dose of RP103 | WBC cystine over time<br>Dosing and exposure of RP103 |
| | **Other End Points** | Kidney function, somatic growth, BMI, patient QoL (as assessed by PedsQL 4.0)<br>Harms | Adverse events |
| NOTES | **Publications** | Clinical study report (RP103-04)[35] | Preliminary report[57] |

BMI = body mass index; eGFR = estimated glomerular filtration rate; mos = months; NA = not applicable; nmol = nanomoles; PK = pharmacokinetics; q.6.h. = every 6 hours; q.12.h. = every 12 hours; PedsQL 4.0 = Pediatric Quality of Life Inventory; PK = pharmacokinetics; pts = patients; QoL = quality of life; WBC = white blood cell; wk = week.

Source: Clinical Study Report;[56] Langman et al.;[35] Preliminary Study Reports.[17,57]

## Table 14: Patient Demographics and Baseline Characteristics – RP103-04

| | RP103 |
|---|---|
| **Number of patients, N** | **60** |
| Male, n (%) | 37 (61.7) |
| Age at start of treatment (yr), mean (SD) | 10.9 (6.0) |
| RP103-naive (newly enrolled), n (%) | 19 (32.2) |
| **Previous dose Cystagon, median (mg/m$^2$/day)** | |
| Previously enrolled in RP103-03 (n = 40) | 1,515.3 |
| Newly enrolled, ≤ 6 years old (n = 13) | 983.3 |
| Newly enrolled, kidney transplant (n = 6) | 1,092.8 |
| **Baseline WBC cystine levels, mean (SD)** | |
| Previously enrolled in RP103-03 (n = 40) | 0.43 (0.513) |
| Newly enrolled, ≤ 6 years old (n = 13) | 1.41 |
| Newly enrolled, kidney transplant (n = 6) | 2.40 |

mg/m$^2$/day = milligrams/metre squared/day; N = total number of patients in study; n = number of patients in subgroup; SD= standard deviation; yr = year.

Source: Clinical Study Report,[56] Langman et al.[35]

## Table 15: Summary of Demographics and Baseline Disease Characteristics of RP103-07

| | All Patients Who Received at Least One Dose<br>N = 41 |
|---|---|
| Age in years, mean (SD) | 24.5 (11.56) |
| Male, n (%) | 20 (48.8) |
| White n (%) | 38 (92.7) |
| Hispanic | 2 (4.9) |
| Black | 1 (2.0) |
| Baseline WBC cystine levels, mean nmol half cystine/mg protein (SD) | 1.403 (1.48) |
| Baseline eGFR, mean mL/min/1.73m$^2$ (SD) | 65.4 (29.88) |
| Mean daily dose Cystagon, mg (SD) | 1,624 (565.61) |

eGFR = estimated glomerular filtration rate; mg = milligram; mL/min/1.73m2 = millilitres/minute/1.73 metres squared; N = total number of patients; n = number of patients in subgroup; nmol = nanomoles; SD = standard deviation; WBC = white blood cell.

Source: Preliminary Study Report[57]

## Table 16: Patient Disposition and Treatment Exposure – RP103-04

| | Overall | Subpopulation | | |
|---|---|---|---|---|
| | | RP103-03 (N = 40) | Age ≤ 6 Yrs (N = 13) | Transplant (N = 6) |
| **Enrolled in extension study** | **60** | **40** | **14** | **6** |
| **Received at least 1 dose of RP103, N** | **59** | **40** | **13** | **6** |
| **Estimated duration of exposure, N (%)** | | | | |
| ≤ 1 yr | 3 (5.1) | 2 (5) | 0 | 1 (16.7) |
| > 1 yr to ≤ 2 yrs | 8 (13.6) | 2 (5) | 5 (38.5) | 1 (16.7) |
| > 2 yrs to ≤ 3 yrs | 21 (35.6) | 15 (37.5) | 4 (30.8) | 2 (33.3) |
| > 3 yrs to ≤ 4 yrs | 18 (28.8) | 12 (27.5) | 4 (30.8) | 2 (33.3) |
| > 4 yrs to ≤ 5 yrs | 9 (15.3) | 9 (22.5) | 0 | 0 |
| **Discontinued before end of study, N (%)** | 30 (51) | NR | | |
| **Participants switched to commercial Procysbi when it became available** | 25 (42) | NR | | |
| **Physician decision** | 1 (2) | NR | | |
| **AE** | 3 (5) | NR | | |
| **Reasons unrelated to AE / wished to withdraw** | 1 (2) | NR | | |

AE = adverse event; NR = not reported; yr = year.

Source: Clinical Study Report,[56] Langman et al.[35]

## Table 17: Patient Disposition in RP103-07

| | All Patients (N = 41) | Cystagon Phase (N = 41) | RP103 Phase (N = 41) |
|---|---|---|---|
| Screened for Eligibility, N | 43 | | |
| **Treated On or After Day 1, N** | **41** | | |
| Cystagon dosing period | 41 | | |
| RP103 dosing period | 41 | | |
| **Study Population, N (%)** | **41 (100)** | **41 (100)** | **41 (100)** |
| Pharmacodynamic | 41 (100) | 41 (100) | 41 (100) |
| Per-protocol | 30 (73.2) | 30 (73.2) | 30 (73.2) |
| Pharmacokinetics | 41 (100) | 41 (100) | 41 (100) |
| Safety | 41 (100) | 41 (100) | 41 (100) |
| **Withdrew Prior to Study Completion, N (%)** | **2 (4.9)** | | |
| Withdrawal during either treatment phase | 0 (0) | | |
| Withdrawal during long-term phase | 2 (4.9) | | |
| **Reason for withdrawal** | | | |
| Non-compliance | 1 (2.4) | | |
| Patient withdrew consent | 1 (2.4) | | |

N = total number of patients.

Source: Preliminary Study Report[57]

## Table 18: Treatment Exposure in Safety Analysis Set in RP103-07

| Parameter | Cystagon Phase (N = 41) | RP103 Phase (N = 41) | Long-Term Phase (N = 41) |
|---|---|---|---|
| Duration of study drug exposure, mean days (SD) | 91 (5.64) | 117.7 (8.24) | 167.0 (153.08) |
| Duration of study drug exposure, median days (range) | 91 (82,108) | 119.0 (98,137) | 168.0 (1, 511) |
| Days with a missed dose, mean days (SD) | 10.9 (17.59) | 11.9 (17.52) | 26.2 (64.48) |
| Ratio of days with a missed dose to duration of exposure, mean (SD) | 0.1 (0.18) | 0.1 (0.15) | 0.1 (0.21) |
| Comparison of ratios between Cystagon vs. RP103, *P* values | 0.6857 | | |

SD = standard deviation.

Source: Preliminary Study Report.[57]

### Efficacy

*RP103-04*

Long-term efficacy was summarized for each parameter based on patients who remained in the study during the open-label period and who had data at the reported collection time points. Patients were stratified by subgroup (previous patients in RP103-03; patients less than and equal to 6 years of age; post-renal transplant patients). Overall, WBC cystine levels were able to stay below 1 nmol half cystine/mg protein for patients extending therapy, and were able to decrease steadily for newly enrolled patients over the length of the study (mean [SD] of 0.54 [0.393] at approximately 3.75 years).[6,17] Additionally, the total daily dose of RP103 at month 1 was 82% of the previous Cystagon total daily dose and the RP103 dose level was generally maintained over the duration of the study, indicating that the long-term administration of RP103 did not require an increase in the daily dose requirement over time.[6] For newly enrolled patients less than and equal to 6 years of age (n = 13), the initial starting dose was 70% of the Cystagon dose at time of entry to study. The mean dose for this subpopulation was generally stable over time. For newly enrolled patients who had previous renal transplantation, the initial dose (70% of the Cystagon dose at time of entry) and mean RP103 dose level increased somewhat over time at later visits throughout the study. These efficacy outcomes also improved throughout the long-term trial period and are summarized in Table 19.[6,17]

In regard to secondary outcomes, renal function was preserved throughout the study time period, with no significant differences with respect to eGFR, with respect to patients less than and equal to 6 years of age as well as patients who were transplant recipients. In regard to height z score, a growth retardation was found in patients at baseline (–1.54) which is to be expected as part of disease pathogenesis. Due to maintenance of WBC cystine levels below a target of less than 1 nmol half cystine/mg protein, this growth trajectory was sustained throughout treatment. A VAS, which was used to assess pain-associated swallowing difficulty, was measured on a 0 to 10 metric. It was reported that the mean changes from baseline in this metric were generally small over the course of this study and no distinct trends were reported. Lastly, quality of life was assessed with either the PedsQL 4.0 for patients less than 19 years of age), or the Short Form 36 (SF-36) for patients greater than and equal to 19 years of age instrument. For the PedsQL 4.0, the mean per cent change showed an improvement in functionality relative to the baseline scores documented in RP103-03 in all five categories (Physical, Emotional, Social, School and Total) at the first visit in month 1 of RP103-04, and this improvement was maintained

from baseline across the four-year duration of the study. Secondary efficacy outcomes are summarized in Table 20.[6,17]

*RP103-07*

For both Cystagon and RP103 treatment phases, WBC cystine levels remained within a relatively narrow range for the majority of patients. Preliminary results are fully summarized in Table 21. The average WBC cystine value was found to be closer to the less than 1 nmol half cystine/mg protein target in patients during the Cystagon treatment phase of the study than in the RP103-treatment phase of the study.[57] During the Cystagon phase, non-morning WBC cystine was on average 0.213 nmol half cystine/mg protein lower than the corresponding morning WBC cystine level during the RP103 phase.[57] In the per-protocol population, the variability in WBC cystine levels between the morning and non-morning samples was found to be significantly lower in patients during their treatment with RP103 than during treatment with Cystagon ($P$ = 0.0081).[57]

Dosing compliance, which was measured by the number of days with one or more missed doses, was similar during the Cystagon and RP103 phases. The mean average daily dose during the three-month Cystagon phase was 1,624 mg. The mean average daily dose during the subsequent three-month RP103 phase was 1,168 mg (72% of the mean dose during the Cystagon phase). The median duration of RP103 exposure during the long-term phase as of the interim data cut-off date of 10 April 2015 was 168 days.[17,57]

## Table 19: RP103-04 Extension Main Efficacy Outcomes Over Time

| Visit | Approximate Yrs in Study | Subgroups | | |
|---|---|---|---|---|
| | | WBC Cystine (nmol half cystine/mg protein) | | |
| | | RP103-03 (N = 40) Mean (SD), [n] | Age ≤ 6 Yrs (N = 13) Mean (SD), [n] | Transplant (N = 6) Mean (SD), [n] |
| Baseline[a] | 0 to 0.1 yr | 0.43 (0.513) [n = 39] | 1.41 (1.030) [n = 13] | 2.40 (1.687) [n = 5] |
| Monthly visit 6 | 0.5 yr | 0.46 (0.431) [n = 38] | 2.00 (1.729) [n = 13] | 1.75 (1.242) [n = 5] |
| Quarterly visit 2 | 1.0 yr | 0.42 (0.352) [n = 38] | 1.10 (0.578) [n = 12] | 1.28 (0.830) [n = 5] |
| Quarterly visit 4 | 1.5 yrs | 0.49 (0.344) [n = 37] | 1.31 (1.480) [n = 11] | 1.57 (0.944) [n = 4] |
| Quarterly visit 6 | 2.0 yrs | 0.52 (0.304) [n = 35] | 1.40 (2.188) [n = 6] | 0.62 (0.368) [n = 3] |
| Quarterly visit 8 | 2.5 yrs | 0.44 (0.371) [n = 29] | 0.98 (0.487) [n = 6] | 0.84 (0.550) [n = 3] |
| Quarterly visit 10 | 3.0 yrs | 0.39 (0.290) [n = 20] | 0.90 (0.386) [n = 3] | 1.69 (0.682) [n = 3] |
| Quarterly visit 13 | 3.75 yrs | 0.54 (0.393) [n = 19] | NA | NA |
| | | Mean RP103 Dose (mg/m$^2$/day) Over Time | | |
| | | RP103-03 (N = 40) Mean (SD), [n] | Age ≤ 6 Yrs (N = 13) Mean (SD), [n] | Transplant (N = 6) Mean (SD), [n] |
| Baseline[a] | 0 to 0.1 yr | 1,275.99 (242.663) [n = 39] | 813 (251.494) [n = 13] | 868.52 (273.369) [n = 5] |
| Monthly visit 6 | 0.5 yr | 1,258.08 (299.656) [n = 38] | 914.46 (286.071) [n = 13] | 783.41 (320.949) [n = 5] |

| Visit | Approximate Yrs in Study | Subgroups | | |
|---|---|---|---|---|
| Quarterly visit 2 | 1.0 yr | 1,232.76 (344.772) [n = 38] | 910.60 (285.206) [n = 12] | 911.90 (330.893) [n = 5] |
| Quarterly visit 4 | 1.5 yrs | 1,224.76 (350.318) [n = 36] | 938.04 (252.093) [n = 11] | 792.49 (276.809) [n = 4] |
| Quarterly visit 6 | 2.0 yrs | 1,196.78 (350.307) [n = 35] | 932.63 (244.550) [n = 6] | 1,109.35 (333.238) [n = 3] |
| Quarterly visit 8 | 2.5 yrs | 1,116.18 (349.867) [n = 29] | 829.93 (213.787) [n = 6] | 1,086.34 (313.558) [n = 3] |
| Quarterly visit 10 | 3.0 yrs | 1,079.56 (225.781) [n = 29] | 765.75 (240.093) [n = 3] | 1,091.81 (335.229) [n = 3] |
| Quarterly visit 13 | 3.75 yrs | 996.24 (274.637) [n = 17] | NR | NR |

[a] Baseline refers to measurements or means taken from the first available visit in month 1 for patients from RP103-03 and day 1 for the other two subpopulations. For day 1, the WBC cystine value immediately prior to the RP103 dose was summarized.

N = total number of patients; n = number of patients in subgroup; NR = not reported; nmol = nanomoles; SD = standard deviation; yr = year.

Source: RP103-04 Clinical Study Report.[56]

## Table 20: RP103-04 Extension Efficacy Outcomes – Individual Parameters

| Visit | Approximate Years in Study | Subgroups | | |
|---|---|---|---|---|
| | | Renal Function (eGFR) | | |
| | | RP103-03 (N = 40) Mean (SD), [n] | Age ≤ 6 Yrs (N = 13) Mean (SD), [n] | Transplant (N = 6) Mean (SD), [n] |
| Baseline[a] | 0 to 0.1 yr | 66.04 (26.326) [n = 38] | 74.13 (26.131) [n = 13] | 71.68 (24.374) [n = 6] |
| Monthly visit 6 | 0.5 yr | 61.23 (24.861) [n = 38] | 73.01 (26.896) [n = 13] | 53.89 (18.907) [n = 5] |
| Quarterly visit 2 | 1.0 yr | 58.31 (22.479) [n = 38] | 67.87 (24.759) [n = 13] | 55.70 (17.967) [n = 5] |
| Quarterly visit 4 | 1.5 yrs | 58.80 (23.650) [n = 38] | 72.37 (24.831) [n = 13] | 57.79 (25.587) [n = 5] |
| Quarterly visit 6 | 2.0 yrs | 56.11 (24.576) [n = 35] | 77.08 (25.918) [n = 6] | 70.02 (30.519) [n = 3] |
| Quarterly visit 8 | 2.5 yrs | 59.17 (26.789) [n = 29] | 71.27 (23.826) [n = 6] | 76.21 (36.561) [n = 3] |
| Quarterly visit 10 | 3.0 yrs | 60.87 (26.602) [n = 21] | 65.69 (15.203) [n = 4] | 75.73 (36.174) [n = 3] |
| Quarterly visit 13 | 3.75 yrs | 57.24 (25.012) [n = 20] | NA | NA |
| | | Height z Score for Age and Gender in Patients ≤ 12 Yrs (N = 38) | | |
| | | Mean (SD) [n] | | |
| Baseline[a] | 0 to 0.1 yr | –1.54 (1.016) [n = 38] | | |
| Monthly visit 6 | 0.5 yr | –1.45 (1.037) [n = 37] | | |
| Quarterly visit 2 | 1.0 yr | –1.51 (1.083) [n = 37] | | |
| Quarterly visit 4 | 1.5 yrs | –1.60 (1.063) [n = 37] | | |
| Quarterly visit 6 | 2.0 yrs | –1.73 (0.987) [n = 30] | | |
| Quarterly visit 8 | 2.5 yrs | –1.77 (1.197) [n = 24] | | |
| Quarterly visit 10 | 3.0 yrs | –1.71 (0.782) [n = 16] | | |
| Quarterly visit 13 | 3.75 yrs | –1.80 (0.995) [n = 11] | | |

[a] Baseline refers to measurements or means taken immediately prior to enrolment into RP103-04. All time points do not refer to time after initiation of RP103 treatment, but to time in the extension period.

eGFR = estimated glomerular filtration rate; N = total number of patients; n = number of patients in subgroup; SD = standard deviation; yr = year.

Source: Clinical Study Report.[56]

## Table 21: Primary Outcomes and Associated Individual Parameters in RP103-07 Trial Assessed in Pharmacodynamic Population

| Parameter | Cystagon Treatment Phase | RP103 Treatment Phase | One–Sample t-Test Two-Sided *P* Value | Paired t-Test Two-Sided *P* Value |
|---|---|---|---|---|
| | N = 41 | N = 40 | | |
| **WBC cystine level, nmol half cystine/mg protein** | | | | |
| Mean morning value at end of treatment phase (SD) | 1.068 (1.3162) | 1.467 (1.7972) | | |
| Mean evening value at end of treatment phase (SD) | 1.160 (1.6296) | 1.473 (1.6460) | | |
| **Difference in morning and non-morning WBC cystine values** | | | | |
| Mean difference between morning and non-morning WBC cystine values (SD) | –0.213 (0.5490) | 0.033 (0.5513) | 0.0186 | 0.7047 |
| Mean difference between morning and non-morning log WBC cystine values (SD) | –0.200 (0.4850) | 0.087 (0.3981) | | 0.0081 |
| Mean difference between morning and non-morning log WBC cystine values, per-protocol population (SD) | –0.101 (N = 30) | 0.171 (N = 30) | | 0.0167 |
| **Daily dose over treatment phases, mean (SD)** | 1,624 (565.61) | 1,168 (473.84) | | |
| **Concurrent use of gastric acid-reducing medication** | | | | |
| At least 1 gastric acid-reducing concomitant medication (SD) | 21 (51.2) | 21 (51.2) | | |
| Days of usage of gastric acid-reducing concomitant medication, mean (SD) | 91.24 (7.520) | 90.71 (37.140) | | |
| **Estimated Glomerular Filtration Rate, mL/min/1.73m$^2$** | | | | |
| Mean value at end of treatment phase (SD) | 64.3 (28.32) | 62.6 (30.51) | | |
| Change from baseline at end of treatment phase (SD) | –1.0 (10.08) | –2.6 (10.39) | | |

mL/min/1.73m$^2$= milligram/minute/1.73 metres squared; N = total number of patients; nmol= nanomoles; SD = standard deviation; WBC = white blood cell.
Source: Clinical Study Report.[35]

## Harms

### *RP103-04*

Total reported adverse events in RP103-04 are summarized in Table 22. Of the 59 patients participating in the RP103-04 extension, all but two patients (97%) experienced at least one treatment-emergent adverse event (TEAE). The most commonly reported adverse events included: vomiting (66.6%); headache (30.5%); diarrhea (22%); nausea (22%); influenza (20%); gastroenteritis, abdominal pain, upper respiratory tract infection (16.9% each). There were no deaths during the study. Three patients who were previously enrolled in RP103-03 experienced at least one TEAE which led to discontinuation from the study. These included one 14-year-old female who discontinued due to Grade 2 vomiting, a seven-year-old male who discontinued due to Grade 1 dyspepsia and Grade 1 decreased appetite, and a 15-year-old male who discontinued due to Grade 3 renal failure.[56]

### *RP103-07*

The harms reported in this study are summarized in Table 22. In comparing the initial Cystagon and RP103 treatment phases, there was a higher incidence of mild to moderate gastrointestinal adverse events during the RP103 treatment phases. Four patients reported at least one TEAE related to study drug in the Cystagon treatment phase, compared with 19

patients in the RP103 treatment phase, No patients discontinued treatment due to an adverse event.[57]

There were eight serious TEAEs that occurred during the Cystagon phase, one of which was assessed to possibly be related to Cystagon treatment. There was no dosage adjustment made to treatment, and the adverse event was reported to have resolved. There were 12 serious TEAEs which occurred during the RP103 phase, two of which were considered to possibly be associated with RP103 treatment. One of these events was a case of diarrhea and another was a case of abdominal pain, both of which did not result in a dosage change and both of which were reported to be resolved or recovered at a later date. Six patients were reported to have serious TEAEs occurring in the long-term phase. All these incidences were reported to be unlikely related or unrelated to RP103 treatment and all had an outcome of resolved, either with or without sequelae.[57]

## Table 22: Harms Within Safety Population of Additional Studies

| | RP103-04 | | | | RP103-07 | | |
|---|---|---|---|---|---|---|---|
| | Overall | Continued from RP103-03 | Age ≤ 6 Yrs | Transplanted | Cystagon Phase | RP103 Phase | Long-Term Phase |
| | N = 59 | N = 40 | N = 13 | N = 6 | N = 40 | N = 41 | N = 41 |
| Pts with TEAE, N (%) | 57 (96.6) | 40 (100) | 13 (100) | 4 (66.7) | 31 (75.61) | 37 (90.24) | 23 (56.10) |
| Pts with Serious TEAE, N (%) | 29 (49.2) | 21 (52.5) | 7 (53.8) | 1 (16.7) | 5 (12.20) | 7 (17.07) | 6 (14.63) |
| Pts with drug-related TEAE, N (%) | 35 (59.3) | 28 (70.0) | 5 (38.5) | 2 (33.3) | 4 (9.76) | 19 (46.34) | 5 (12.20) |
| Pts with TEAE leading to withdrawal, N (%) | 3 (5.1) | 3 (7.5) | 0 | 0 | 0 | 0 | 0 |
| Pts with Grade 3 (Severe) TEAE, N (%) | 21 (35.6) | 14 (35.0) | 5 (38.5) | 2 (33.3) | | | |

N = total number of patients; pts = patients; TEAE= treatment-emergent adverse event; yrs = years.

Source: Clinical Study Report,[56] Langman et al.;[16] Preliminary Study Reports[17,57]

### Limitations

*RP103-04*

The main limitation associated with this study was that it included a select population which elected to continue treatment with RP103. As a result, this extension study risks compromising a population of patients who would be more likely to respond to and tolerate RP103, thus decreasing the generalizability to all patients who may benefit from this treatment.

In the trial summarized above, it is difficult to identify whether there is a cause-and-effect relationship between RP103 and its reported efficacy and safety outcomes, as it was not a controlled trial. Furthermore, due to the open-label trial design, in which both the investigators and the patients were unblinded to treatment allocation, it is difficult to determine whether the reporting of adverse events by patients or the assessment of adverse events by investigators could have been influenced. Finally, smaller sample sizes make statistical calculations difficult and limit the interpretability of results.

*RP103-07*

This was an open-label, crossover, single-arm design study which sought to test superiority of intra-patient variance in WBC cystine levels through 24 hours, as well as to follow long-term outcomes for efficacy, safety, and pharmacokinetics of the twice-daily regimen of RP103. Due to the crossover design of the study between active therapies, there is a risk of bias favouring RP103 due to carryover effects from Cystagon therapy. Although the half-life of Cystagon is known to be six hours, it is difficult to rule out that any clinical changes seen in this study may be due to the patient initially being on stable Cystagon therapy. Therefore, in the period of time in which this drug was studied, effects observed after the crossover period risk being falsely attributed to RP103. This issue is compounded by the fact that this study is uncontrolled, increasing difficulty in assessing the true clinical effect of RP103. If there happens to be no change in parameters after the crossover period, it is more difficult to distinguish between treatment effect and no effect at all.

Furthermore, this study found a significantly lower within-patient difference between morning and non-morning WBC cystine levels when patients were treated with RP103, which is not known to be a clinically relevant outcome. While it is established that maintaining a target WBC cystine less than and equal to 1 nmol half cystine/mg protein is associated with a delay in long-term disease progression,[1,3,13,50] it is not known whether reducing the variance of this value will pose any discernable benefit to patients with nephropathic cystinosis. In fact, patients in this study had a higher average WBC cystine value while using RP103 than they did using Cystagon (1.467 versus 1.068 nmol half cystine/mg protein), which is known to be associated with worse long-term outcomes in this patient population. With regard to relevant clinical outcomes such as renal function and height scores, the results were difficult to interpret due the dropout rate over time. Finally, the lack of blinding in this study may have impacted the reporting of adverse events which were reported with regard to frequency and magnitude.

Additional limitations of this study include: an unclear history of nephropathic cystinosis in this patient population, and small patient numbers. Finally, quality of life questionnaires and swallowing assessments were reported to be recorded outcomes in this study, but the results of these were not provided in the preliminary document.[57]

## Summary

*RP103-04*

The objective of this long-term study was to acquire data on the efficacy, safety, and tolerability of RP103 administered every 12 hours to patients with nephropathic cystinosis over a course of two years and greater. After the pivotal study, the study population was extended to include patients less than seven years of age and patients who had previously undergone a renal transplant. It was demonstrated that the long-term use of RP103 was associated with WBC cystine levels that remained within the desired target of less than and equal to 1 nmol half cystine/mg protein. However, the majority of patients (97%) experienced adverse events. Commonly reported adverse events were: vomiting, diarrhea, headache, and nausea. It was hypothesized by investigators that the adverse events experienced by patients may be related to the clinical disease; however medication involvement cannot be ruled out. Limitations of this study were its open-label and single-arm design, without a control group.

*RP103-07*

Results from this phase IIIb international, multi-centre, open-label, uncontrolled, long-term efficacy, safety and pharmacokinetic trial suggest that RP103 has reduced variability of WBC cystine (as measured by mean within-patient difference between morning and evening WBC cystine level) during RP103 treatment compared with Cystagon treatment. However, the absolute values of WBC cystine were lower during the Cystagon treatment phase, which was more closely in line with a target clinical value of less than and equal to 1 nmol half cystine/mg protein in patients with nephropathic cystinosis.

In this trial, the majority of patients (90.2%) experienced adverse events during the RP103 phase of the study. Commonly reported adverse events occurring in this trial were: diarrhea, vomiting, abdominal pain, and nausea. No deaths occurred during the trial, although it was noted that there was a death of a patient that occurred subsequent to study completion, due to trauma.

It is of note that the long-term outcomes in this trial still offer limited interpretability due to the uncontrolled, unblinded nature of the study.

# Appendix 6: Summary of Retrospective Cohort Study

## Aim

To summarize the details and findings of a retrospective analysis conducted by Brodin-Sartorius et al.[22]

## Background

The manufacturer provided a retrospective cohort study by Brodin-Sartorius et al., of 86 nephropathic cystinosis patients (aged ≥ 15 years old) diagnosed in France between 1961 and 1995, as the clinical basis for the time to event data used to populate the pharmacoeconomic model.[22] Patient data were collected retrospectively from two hospitals (l'hôpital Edouard Herriot [Lyon] and l'hôpital Necker-Enfants malades [Paris]) by asking pediatric and adult nephrologists about their patients.

## Results

Immediate-release cysteamine therapy was administered to 75 patients (87%) starting at a mean age of 9.9 years (median 4.3 years; range 0.9 years to 38.6 years) for a mean duration of 17.4 years (median 18.4 years; range 0.9 years to 28.4 years). Patients were divided into three subgroups: a group that started treatment before age 5 years (n = 40 patients); a group that started treatment at or after age 5 years (n = 8 patients); and a group that was untreated prior to the development of end-stage renal disease (ESRD) (n = 38 patients). Twenty-seven patients in the latter subgroup started cysteamine treatment at a mean age of 23 years (median 22.1 years; range 18.9 years to 24.8 years); 11 patients in this group never received cysteamine.

Physician-reported adherence to therapy was reported as "good" for 26 patients (34.6%) and "quite good" for 31 patients (41.3%). A total of 21 patients (28%) had "extended periods without treatment," and seven patients were missing adherence information. Mean white blood cell (WBC) cystine level recorded in 78 patients during the overall follow-up was less than 2 nmol half cystine/mg protein for 22 patients (28.2%), between 2 and 3 nmol half cystine/mg protein for 27 patients (34.6%), and greater than 3 nmol half cystine/mg protein for 29 patients (37.2%).

The outcomes were the occurrence of survival, renal complications (primarily ESRD), extrarenal complications (hypothyroidism, neuromuscular disorder, or diabetes), and socioprofessional outcomes.

Twenty-four patients in the cohort died (27.9%): of those, seven (29.2%) never received treatment, two (8.3%) started cysteamine before 5 years of age, and 15 (62.5%) who started cysteamine after 5 years of age. Seven patients who were never treated (7/11; 64%) died during the study. Survival was significantly improved in the patients treated before the age of 5 years when compared with those not treated (log-rank $P = 0.03$). Patients who started cysteamine after 5 years of age also had significantly improved survival compared with untreated patients (log-rank $P < 0.05$).

Cysteamine therapy initiated before the age of 5 years significantly decreased the incidence of ESRD compared with those who were untreated and those who started after 5 years. The

mean age at ESRD onset was 13.4 ± 4.8 years (median 12.2 years) in the group that started treatment before 5 years of age, and 9.6 ± 2.6 years (median 9.5 years) in the group that started treatment after 5 years of age ($P < 0.05$). Kaplan–Meier survival curves showed that starting cysteamine therapy before the age of 5 years significantly delayed the ESRD onset (log-rank $P <0.0001$) relative to those who started after age 5 years. Patients rated by their physicians as having good adherence had significantly delayed ESRD in comparison with patients with lower adherence or those not treated (log-rank $P < 0.0001$).

A significant delay in the occurrence of neuromuscular disorders, hypothyroidism, and diabetes in nephropathic cystinosis patients treated with cysteamine before the age of 5 years compared with untreated patients (log-rank, $P < 0.001$), was also reported. A statistically significant delay in diabetes and hypothyroidism was reported for patients who started treatment after the age of 5 years compared with the untreated group ($P < 0.001$).

## Limitations

The identification of patients for inclusion in the cohort (i.e., patients with a diagnosis of nephropathic cystinosis) appeared to be appropriate, and was based on the presence of corneal cystine deposits and/or an elevated WBC cystine level of greater than 3 nmol half cystine/mg protein. However, it is not clear if the cohort comprised all patients aged greater than and equal to 15 years of age with a diagnosis of nephropathic cystinosis between 1961 and 1995 seen at the specified two hospitals in France, or if there were any exclusions. Also, the article provides minimal information on the exact sources of data for the study, other than stating that “data were collected from historically referent hospitals (Lyon–Herriot and Paris–Necker Hospital),” and “pediatric and adult nephrologists were asked about their patients.”[22] Therefore it was not possible to assess the validity of the data sources.

It is uncertain whether the seemingly small number of patients in the untreated group (n = 11) and within each of the three subgroups (e.g., a total of eight patients in the group that initiated treatment at greater than and equal to 5 years of age) was truly sufficient for the statistical comparisons. Statistically significant comparisons with small *P* values were reported for many of the comparisons, suggesting that statistically there were enough patients in the study groups to detect a difference beyond chance. It was also reported that adjustments for multiplicity were performed: for example, pairwise comparisons were adjusted with the Hochberg approach and Kaplan–Meier analyses with overall log-rank testing and Bonferroni method for two-by-two comparisons were used for time to event analyses. However, no additional information was provided as to whether the reported *P* values were the adjusted values, and given the number of comparisons made there is a high probability of type I error inflation if the comparisons were not adequately adjusted for multiple comparisons. Moreover, most of the comparisons were based on hypothesis tests with *P* values but standard errors and confidence intervals were not reported, making it difficult to evaluate the precision and the clinical relevance of the statistical findings.

The small numbers likely also limited the investigators’ ability to examine and statistically adjust for confounders and/or effect modifiers. It appeared that all analyses were unadjusted, producing crude estimates. The investigators did test for differences between groups with respect to baseline characteristics, and identified statistically significant differences between the subgroups for age, number of follow-up years, and number of nephropathic cystinosis-related complications. There are limitations to conducting hypothesis tests on baseline characteristics (e.g., not fulfilling certain underlying assumptions for the tests); however, the fact that no evaluation of the potential impact of

differences in baseline characteristics (e.g., effect modifiers) was undertaken, means that there is some possibility that the results could be explained by other factors.

As mentioned, the sources for information were vaguely described in the article. Therefore a key point in the analysis, proper classification of patients based on exposure, is uncertain. Hence, it is difficult to state with certainty, based on the information reported, that exposure misclassification did not occur. With respect to the outcomes, the description of outcome assessment suggested that outcomes were assessed in a clinically appropriate manner. Given that the outcomes are based on reasonably objective measures, it is unlikely that misclassification of outcome occurred.

Survival bias, as acknowledged by the authors, is a possibility in this study. The time frame for the analysis spanned 34 years; therefore there is a reasonable probability that there were cohort period differences. The earliest diagnosed patients in the 1960s would have had different disease management and supportive care than those diagnosed closer to 1995 (e.g., improvement in supportive treatment for renal and extrarenal complications), which could potentially have contributed to higher survival rates for patients diagnosed later in the study.

A key component of the analysis was an assessment of patient adherence to cysteamine treatment. Adherence was measured in the study based on physician questioning of patients, coded in loosely defined categories: “good,” “quite good,” or “extended period without treatment.” No information was provided on whether this was validated or if coding was verified. Therefore, adherence may have been misclassified.

## Conclusions

Brodin-Sartorius et al. present a long-term study on the impact of cysteamine therapy on nephropathic cystinosis complications. The data suggest that cysteamine delays death and other complications of nephropathic cystinosis but does not prevent them. There were some key limitations to the study, as mentioned. However, the results of the study are generally consistent with clinical practice, as described by the clinical expert involved in the CDR review. In particular, earlier initiation of cystine-depleting treatment appears to have an impact on delaying death and complications associated with nephropathic cystinosis.

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