CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Cysteamine 3.8 mg/mL ophthalmic solution (Cystadrops)

(Recordati Rare Diseases Canada Inc.)

Indication: Treatment of corneal cystine crystal deposits in adults and children from two years of age with cystinosis

Service Line:	CADTH Common Drug Review
Version:	Final (with redactions)
Publication Date:	July 2019
Report Length:	84 Pages

CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

CADTH

Table of Contents

Tables

Figures

Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
CCCD	corneal cystine crystal deposit
CCCS	corneal cystine crystal score
CH	cysteamine hydrochloride
CHOC	cysteamine hydrochloride for nephropathic cystinosis
CI	confidence interval
EMA	European Medicines Agency
FA	full analysis
GEE	generalized estimating equation
IOP	intraocular pressure
ITT	intention to treat
IVCM	in vivo confocal microscopy
LADR	local adverse drug reaction
LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution
OCT	optical coherence tomography
OCT-1	adaptive dose regimen of Cystadrops for corneal crystal deposits and ocular manifestations in nephropathic cystinosis
OL	open label
PP	per-protocol
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
WDAE	withdrawal due to adverse event

Drug	Cysteamine ophthalmic solution (Cystadrops)
Indication	Treatment of corneal cystine crystal deposits in adults and children from two years of age with cystinosis
Reimbursement Request	As per indication
Dosage Form(s)	Solution / 3.8 mg/mL
NOC Date	February 11, 2019
Manufacturer	Recordati Rare Diseases Canada Inc.

Executive Summary

Introduction

Cystinosis is a rare, hereditary disease characterized by the accumulation of cystine, which is formed by the oxidation of the amino acid cysteine, in all cells and tissues of the body.[1,2] The two earliest manifestations of cystinosis are renal dysfunction and accumulation of corneal cystine crystals deposits (CCCDs) leading to photophobia. The most severe form of cystinosis, infantile nephropathic cystinosis, makes up approximately 95% of cystinosis cases[1,3] CCCDs in these patients are typically observable by 18 months of age and photophobia from CCCDs appears in about 50% of patients from mid-childhood to adolescence.[2] Juvenile or intermediate nephropathic cystinosis is diagnosed in late childhood or adolescence and is associated with a slower progression of symptoms than in infantile cystinosis.[1,2] Ocular or non-nephrotic cystinosis is characterized by adult onset with CCCDs as the only manifestation.[1]

In addition to photophobia and blepharospasm, reported corneal symptoms include: foreign body sensation, pain, decreased corneal sensitivity, loss of visual contrast sensitivity, and increased glare.[4,5] The following anterior segment complications have also been reported: superficial punctate keratopathy, filamentary keratopathy, band keratopathy, peripheral corneal neovascularization, and corneal thickening.[4,5] According to the clinical experts consulted for this review, not all patients will develop anterior segment complications if the cornea is left untreated.

Cystinosis can be diagnosed through findings of elevated cystine levels in white blood cells or mutations in the gene encoding cystinosin, a lysosomal cystine transporter.[1,3] The presence of CCCDs on slit-lamp examination can provide further evidence for the diagnosis.[1] Oral cystine-depleting therapy with cysteamine is the mainstay of treatment for patients with nephropathic cystinosis, but it does not reach the avascular cornea and therefore is not effective in treating CCCDs.[1,3] Topical ophthalmic solutions of cysteamine hydrochloride (CH) are recommended for treating the cornea.[1,3] According to the clinical experts consulted for the review, Canadian patients with CCCDs are treated with pharmacy-compounded solutions of 0.55% CH with a dosage regimen of one drop per eye every one to two hours during the waking day.

Cystadrops is indicated for the treatment of CCCDs in adults and children from two years of age with cystinosis. Cysteamine reduces corneal cystine crystal accumulation acting as a cystine-depleting agent by converting cystine to cysteine and cysteine-cysteamine mixed disulfides.[6] Cystadrops is a viscous topical ophthalmic solution containing 3.8 mg/mL

cysteamine (0.55% CH). The recommended dosage is one drop in each eye, four times a day during waking hours.[6] The dose could be decreased progressively (to a minimum total daily dose of one drop in each eye) depending on the results of ophthalmic examination (such as CCCD, photophobia).[6]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of cysteamine 3.8 mg/mL (CH 0.55% by weight) ophthalmic solution (Cystadrops) for the treatment of CCCDs in adults and children from two years of age with cystinosis.

Results and Interpretation

The systematic review identified one open-label (OL), parallel-group, phase III randomized controlled trial (RCT). The manufacturer-sponsored Cysteamine Hydrochloride for nephrOpathic Cystinosis (CHOC) study (N = 32, conducted in 2013 at two centres in France by Orphan Europe SARL [part of the Recordati Group]) randomized patients (1:1) to one of two topical cysteamine hydrochloride ophthalmic solutions: a viscous cysteamine 3.8 mg/mL (equivalent to CH 0.55%) solution (Cystadrops) and a CH 0.10% solution. Patients and investigators were not blinded to treatment assignment. Patients were two years of age or older, had a diagnosis of nephropathic cystinosis, and had CCCDs demonstrated by slit-lamp examination. Patients received study treatment for 90 days, with study visits at day 30 and day 90 and no screening or follow-up period. The objective of the CHOC study was to study the efficacy and safety of CH 0.55% versus CH 0.10% in patients with nephropathic cystinosis.

The primary end point of the CHOC study was change in corneal cystine crystal density, as assessed using in vivo confocal microscopy (IVCM) total score, from baseline to day 90. IVCM is a microscopy technique able to directly visualize corneal cystine crystals. Investigators acquired and selected five to 10 IVCM images with a field of view of 0.4 mm × 0.4 mm from each of seven corneal layers in the central cornea for rating by a reader blinded to treatment assignment. The image rating scale ranged from 0 to 4 (0 = no crystals; 1 = less than 25% of deposits; 2 = 25% to 50% of deposits; 3 = 50% to 75% of deposits; 4 = 75% to 100% of deposits) and a total score was obtained by summing up the individual layer scores. IVCM total score had a range of 0 to 28 with higher scores indicating greater crystal density and/or burden. Corneal cystine crystal density was also assessed by slit-lamp examination using the cystinosis corneal crystal score (CCCS) on a scale of 0 to 3 with 0.25 increments based on a library of reference slit-lamp photographs. The thickness of the corneal crystal layer was measured on optical coherence tomography (OCT) images of the central cornea. For all three outcomes, a higher value corresponded to greater corneal crystal burden. In terms of ocular symptoms, photophobia was assessed using both a patient-rated and an investigator-rated scale (ordinal values from 0 to 5, with higher scores corresponding to more severe photophobia). In addition to adverse event (AE) reporting, local adverse drug reactions (LADRs) were recorded in patient diaries following each instillation. Similar outcomes were assessed in a long-term single-arm manufacturer-sponsored study of eight patients receiving Cystadrops for 60 months (the OCT-1 study).

There were a number of limitations affecting the ability to determine the clinical significance of the efficacy results, particularly in relation to the standard of care in Canada. Cystadrops is indicated for the treatment of CCCDs and is expected to provide clinical benefit in improvement in cystinosis-related ocular symptoms through a reduction in these deposits. There was limited evidence, in the form of weak to moderate correlations with an

unvalidated patient-rated photophobia scale, found for an association of the measures of corneal cystine crystal burden with symptoms. There was no evidence found for the validity of the patient- and investigator-rated photophobia scales and how they relate to patients' ability to function or quality of life. It was not possible to rule out the potential for bias from the lack of blinding of patients and investigators in the CHOC study for IVCM total score, CCCS, and the photophobia scales. Finally, the comparator in the CHOC study was of a concentration of CH and dosage regimen expected by the clinical experts consulted for this review to be less effective than the treatment regimen typically used in Canada. Its comparison with CH 0.55% does not inform the efficacy of CH 0.55% compared with Canadian topical CH treatment or best supportive care without topical CH treatment.

Efficacy

The primary end point of the CHOC study, change in IVCM total score from baseline to day 90, showed a statistically significantly greater improvement with CH 0.55% versus CH 0.10% (mean difference of –3.84 [95% confidence interval, –5.58 to –2.11]; Table 1). However, a minimal clinically important difference (MCID) for IVCM total score was not found and the clinical significance of this result is unknown.

The results for other outcomes related to corneal crystal burden, CCCS and corneal crystal layer thickness, were consistent with those for IVCM total score (Table 1). However, statistical interpretation of these results was limited by the lack for multiplicity and potential for inflated type I error outside of the primary end point. Mean CCCS improved numerically from baseline to day 90 in the CH 0.55% group and not in the CH 0.10% (mean change of –0.592 [standard deviation or SD of 0.523] versus 0.105 [SD of 0.240]). Mean crystal thickness by OCT improved numerically from baseline to day 90 in the CH 0.55% group and not in the CH 0.10% group (mean change of –46.3 µm [SD of 55.3 µm] versus 10.6 µm [SD of 43.6 µm]). As with IVCM total score, an MCID was not found for CCCS and corneal crystal layer thickness by OCT. Subgroup analyses in the pediatric and adult populations suggested similar changes in IVCM total score, CCCS, and corneal crystal layer thickness in both populations as in the entire study population.

The clinical experts consulted for this review considered the most important clinical outcome assessed in the CHOC study to be patient-rated photophobia. Mean patient-rated photophobia numerically improved in the CH 0.55% group (mean change of –0.267 and SD of 0.583) and numerically worsened in the CH 0.10% group (mean change of 0.226 [SD of 0.717]; Table 1). The statistical model for these results did not converge and statistical test results were therefore unavailable. In both groups, most patients experienced no change in patient-rated photophobia from baseline to day 90. Numerically higher percentages of patients' eyes in the CH 0.55% group versus the CH 0.10% group had an improvement of 1 point (13.3% versus 9.7%) and 2 points (6.7% versus none). There was a worsening in 25.8% of eyes in the CH 0.10% group and none in the CH 0.55% group.

Photophobia was also rated on a scale of 0 to 5 by investigators (Table 1). Mean investigator-rated photophobia numerically improved in the CH 0.55% group (mean change of –0.633 [SD of 0.765]) and did not change appreciably in the CH 0.10% group (mean change of 0.065 [SD of 0.442] Table 11). Similar trends with respect to individual response were observed with investigator-rated photophobia as with patient-rated photophobia. As with CCCS and corneal crystal layer thickness, statistical interpretation of the photophobia results was limited by the lack of control for multiplicity and potential for inflated type I error. An MCID was not found for either photophobia scale.

With respect to visual function and complications of CCCDs, visual acuity, visual contrast sensitivity, corneal staining, and intraocular pressure (IOP) were assessed. Given the lack of statistical testing for these outcomes, conclusions could not be drawn. The clinical experts consulted for this review did not consider any differences between groups in any of these outcomes to be notable.

Given that patients with cystinosis are expected to require lifelong treatment for CCCDs, the 90-day treatment period in the CHOC study did not provide sufficient evidence for the long-term efficacy and safety of CH 0.55%. The efficacy results in the OCT-1 study suggested that photophobia and corneal cystine crystal burden improved and that this improvement was maintained on average over treatment duration of five years. However, the lack of a control group meant that conclusions could not be drawn regarding long-term efficacy of CH 0.55%.

Harms

In the CHOC study, AEs classified as eye disorders were more common with CH 0.10% (68.8% of patients) than with CH 0.55% (33.3% of patients), with the most common eye disorders being ocular hyperemia, eye pain, and eye irritation (Table 1). According to the clinical experts consulted for this review, the eye disorder AEs were potentially associated with either the disease or the study medication. The only ocular serious AE (SAE) was corneal graft rejection in a patient who initiated study treatment shortly after corneal transplant surgery. There was one withdrawal due to adverse event in the CH 0.55% group due to allergic conjunctivitis that occurred near the end of the treatment period. The clinical experts did not identify any AEs, SAEs, or between-group differences in AEs that were of notable concern.

Local adverse drug reactions (LADRs) upon instillation (stinging, redness, burning, blurred vision, and itching) lasting less than one hour were reported in all patients in the CHOC study receiving CH 0.55% and 68.8% of patients receiving CH 0.10%. Higher percentages of patients in the CH 0.55% group versus the CH 0.10% group experienced LADRs of each severity: 100.0% versus 68.8% for mild, 80.0% versus 37.5% for moderate, 33.3% versus 12.5% for severe, and 13.3% versus 6.3% for unbearable. Higher percentages of patients in the CH 0.55% group than in the CH 0.10% group had stinging (80.0% versus 50.0%), redness (60.0% versus 43.8%), burning (66.7% versus 25.0%), blurred vision (60.0% versus 25.0%), and itching (40.0% versus 25.0%, Table 14).

For LADRs lasting more than one hour, at least one LADR was reported in 33.3% of the CH 0.55% group and 50.0% of the CH 0.10% group (Table 1). While rates of redness (26.7% and 31.3%) and burning (13.3% and 12.5%) were similar between groups, the following LADRs lasting more than one hour were more common in the CH 0.10% group than in the CH 0.55% group: stinging (18.8% versus 6.7%), blurred vision (18.8% versus none), and itching (12.5% versus none).

In the OCT-1 study of eight patients over five years of treatment with CH 0.55%, there was one SAE of concern (corneal neovascularization, which could have been related to disease progression or the study medication). Though the results were not conclusive, reporting of LADRs over the first 24 months of CH 0.55% treatment suggested that LADRs decreased in frequency and/or were perceived by patients to improve with longer durations of treatment.

Place in Therapy

The following is from a summary of input provided by a panel of three clinical experts, two ophthalmologists and one nephrologist, all of whom have experience in treating patients with cystinosis. The full summary of input from the clinical panel is provided in Appendix 2.

Pharmacy-compounded ophthalmic cysteamine solutions are limited by their lack of standardization in active ingredient concentrations and methods of preparation across pharmacies, short shelf life, and regional variations in availability of pharmacies that provide these solutions. The compounded solutions need to be refrigerated at all times when not in use, and patients may unknowingly use eye drops with compromised effectiveness due to inadequate refrigeration. These solutions must be administered very frequently for maximal effectiveness (ideally, every one to two hours during waking hours). Long-term adherence to ophthalmic therapies for other conditions with once a day dosing already tends to be poor and adherence to multiple doses a day is expected to be even worse. As part of the challenges associated with adherence to this dosing regimen, children incapable of self-administration may not be able to adhere to the dosing schedule during school hours. The unmet need currently is having a commercially available, standardized, easy to access topical medication that is dosed less frequently than the compounded drops.

As with current treatment, patients with cystinosis who have ocular symptoms or complications arising from corneal cystine crystal deposition are appropriate candidates for treatment with Cystadrops. All of these patients could potentially benefit from Cystadrops treatment. Almost all patients with cystinosis will develop corneal cystine crystals and, at some point in their lives, photophobia. Cystadrops is unlikely to be used off-label.

Conclusions

Compared with CH 0.10% four times daily, CH 0.55% four times daily results in a reduction in CCCDs over a three-month period in patients with cystinosis. However, the clinical significance of these findings remains unknown due to the lack of established MCIDs for the measures of corneal cystine crystal burden and limited evidence for their association with symptoms. While the results for investigator-rated photophobia, a secondary outcome, suggested a benefit with CH 0.55% over CH 0.10%, there was no control for multiplicity of outcomes, and the validity and MCID of the scale are unknown. Conclusions could not be drawn based on long-term efficacy data from a single-arm, 60-month trial due to the lack of a comparator arm.

Safety data from the RCT and the single-arm trial did not demonstrate any notable AEs, SAEs, or between-group differences in AEs, other than one SAE (corneal neovascularization) that could have been related to disease progression or CH 0.55% treatment. Safety data suggested that LADRs upon instillation lasting less than an hour were more common with CH 0.55% than with CH 0.10%; however, long-term data for CH 0.55% suggest that LADRs may decrease in frequency and/or be perceived by patients to improve with longer durations of treatment.

Table 1: Summary of Results

	CHOC	
Efficacy	**CH 0.55%**	**CH 0.10%**
IVCM total score (primary end point)	**IVCM FA Set N = 22 eyes**	**IVCM FA Set N = 20 eyes**
Mean at baseline (SD)	10.6 (4.18)[a]	10.8 (3.47)
Mean at day 90 (SD)	6.04 (2.08)[a]	9.81 (3.81)[a]
Mean change (SD)	–4.60 (3.12)[a]	–0.455 (3.38)[a]
Difference in mean change, CH 0.55% vs. CH 0.10% (95% CI)	–3.84 (–5.58, –2.11)	
P value	**< 0.0001**	
Corneal cystine crystal score	**FA Set N = 30 eyes**	**FA Set N = 32 eyes**
Mean at baseline (SD)	2.26 (0.563)	1.98 (0.500)[b]
Mean at day 90 (SD)	1.67 (0.729)	2.09 (0.519)[b]
Mean change (SD)	–0.592 (0.523)	0.105 (0.240)[b]
P value	0.0015[c]	
Crystal layer thickness by OCT, µm		
Mean at baseline (SD)	275 (159) N = 30	260 (167) N = 29
Mean at day 90 (SD)	241 (133) N = 28	259 (174) N = 32
Mean change (SD)	–46.3 (55.3) N = 28	10.6 (43.6) N = 29
P value	0.0031[c]	
Photophobia rated by patient		
Mean at baseline (SD)	1.73 (1.31)	1.61 (1.23)[b]
Mean at day 90 (SD)	1.47 (1.17)	1.84 (1.27)
Mean change (SD)	–0.267 (0.583)	0.226 (0.717)[b]
Photophobia rated by investigator		
Mean at baseline (SD)	1.87 (1.17)	1.68 (1.05)[b]
Mean at day 90 (SD)	1.23 (1.17)	1.81 (1.20)
Mean change (SD)	–0.633 (0.765)	0.065 (0.442)[b]
P value	0.0048[c]	
Harms	**Safety Set N = 15 patients**	**Safety Set N = 16 patients[d]**
Patients with > 0 SAEs, N (%)	2 (13.3)	2 (12.5)
Gastroenteritis	1 (6.7)	1 (6.3)
Fatigue	1 (6.7)	0
Corneal graft rejection	0	1 (6.3)
WDAEs, N (%)	1 (6.7)	0
Patients with > 0 AEs, N (%)	10 (66.7)	13 (81.3)
Patients with > 0 notable AEs, N (%)		
Eye disorders	5 (33.3)	11 (68.8)
Ocular hyperemia	4 (26.7)	5 (31.3)
Eye pain	1 (6.7)	3 (18.8)
Eye irritation	2 (13.3)	2 (12.5)
Blurred vision	0	3 (18.8)
Conjunctival hyperemia	1 (6.7)	0
Corneal neovascularization	0	1 (6.3)[e]

	CHOC	
Visual impairment	1 (6.7)	0
Patients with > 0 severe LADRs lasting < 1 hour, N (%)	5 (33.3)	2 (12.5)
Patients with > 0 unbearable LADRs lasting < 1 hour, N (%)	2 (13.3)	1 (6.3)
Patients with > 0 LADRs lasting > 1 hour, N (%)	5 (33.3)	8 (50.0)

Source: Clinical study report for the CHOC study.[7]

AE = adverse event; CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; CI = confidence interval; FA = full analysis; IVCM = in vivo confocal microscopy; LADR = local adverse drug reaction; OCT = optical coherence tomography; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

NOTE: Patients who did not undergo the IVCM procedure at baseline (expected to be younger children) were excluded from the IVCM analysis.

NOTE: For the efficacy outcomes, each pair of eyes was considered as repeated measurements within each patient.

NOTE: For IVCM total score, a generalized estimating equation model was used which included treatment group as a factor and baseline IVCM total score as a covariate. For all other efficacy outcomes, an analysis of covariance model was used which included treatment group as a factor and baseline value as a covariate. The model for photophobia did not converge.

NOTE: Pre-specified LADRs were redness, blurring, itching, stinging, and burning.

[a] IVCM data were missing for one patient in the CH 0.55% group in addition to one patient and one eye in second patient in the CH 0.10% group.

[b] Data were missing for one eye.

[c] *P* values are descriptive only as there was no control for multiplicity of outcomes.

[d] In the CH 0.10% group, 17 patients were randomized, and one patient was lost to follow-up without any data on treatment administration.

[e] Corneal neovascularization was present at baseline.

Introduction

Disease Prevalence and Incidence

Cystinosis is a rare, hereditary disease characterized by the accumulation of cystine crystals in all cells and tissues. Cysteine, an amino acid, oxidizes to form cystine, which accumulates in lysosomes unless transported out by cystinosin. Patients with cystinosis have mutations in the gene encoding cystinosin and there are three main forms of cystinosis.[1] The two earliest manifestations of cystinosis are renal dysfunction leading to end-stage renal disease and accumulation of corneal cystine crystal deposits (CCCDs) leading to photophobia.[1,2] The most severe form of cystinosis, infantile nephropathic cystinosis, makes up approximately 95% of cystinosis cases[1,3] and typically results in renal Fanconi syndrome (involving renal tube dysfunction) by the first year of life and progressive loss of glomerular function with end-stage renal failure before the age of 10 if not treated.[2] CCCDs are typically observable by 18 months of age and photophobia from corneal deposits appears in about 50% of patients from mid-childhood to adolescence.[2] Juvenile or intermediate nephropathic cystinosis is diagnosed in late childhood or adolescence and is associated with a slower progression of symptoms than in infantile cystinosis.[1,2] Ocular or non-nephrotic cystinosis is characterized by adult onset with CCCDs as the only manifestation.[1]

Given its systemic nature, nephropathic cystinosis is associated with a wide range of symptoms and complications. Aside from those manifestations already mentioned, cystinosis can also result in growth retardation, rickets, hypothyroidism, swallowing difficulties, muscle wasting and weakness, myopathy, male hypogonadism, diabetes, and central nervous system involvement.[1,3]

In addition to photophobia and blepharospasm, reported corneal symptoms in patients with cystinosis include: foreign body sensation, pain, decreased corneal sensitivity, loss of visual contrast sensitivity, and increased glare.[4,5] The following anterior segment complications have also been reported: superficial punctate keratopathy, filamentary keratopathy, band keratopathy, peripheral corneal neovascularization, and corneal thickening.[4,5] According to the clinical experts consulted for this review, all patients with cystinosis will experience corneal symptoms, but not all patients will develop anterior segment complications if the cornea is left untreated.

Patient input was not received for the current review. Patient input for a previous CDR of a drug for nephropathic cystinosis indicated that in response to a survey of patients and parents of patients with cystinosis, crystals in the eyes and/or photosensitivity was the most common symptom experienced. In terms of how much the symptom affected them at some point in time, most respondents reported “much or severe” (44%) or “some” (50%).[8]

The annual incidence of cystinosis worldwide is estimated to be approximately one in 100,000 to 200,000 live births.[1,2] Higher than average incidence has been reported in two Canadian subpopulations: French Canadians (approximately 1 in 62,500 live births[9,10]) and the Amish Mennonite community in southwestern Ontario.[11]

Standards of Therapy

Cystinosis can be diagnosed through findings of elevated cystine levels in white blood cells or mutations in the gene encoding cystinosin.[1,3] The presence of CCCDs on slit-lamp examination can provide further evidence for the diagnosis.[1] Oral cystine-depleting therapy with cysteamine has been shown to prolong survival, delay progression of the end-stage renal disease, and reduce the severity and frequency of extrarenal complications.[1,3] It should be initiated as early as possible to prevent complications and it is a lifelong treatment.[1,3] Other medications and supplements for the treatment of symptoms and prevention of growth impairment include nutrient replacements (sodium, potassium citrate, and vitamin D) and growth hormone therapy.[1,3]

Oral cysteamine does not reach the cornea and therefore is not effective in treating CCCDs.[1,3] Topical ophthalmic solutions of cysteamine hydrochloride (CH) are recommended for treating the cornea.[1,3] According to the clinical experts consulted for the review, Canadian patients with CCCDs are treated with pharmacy-compounded solutions of 0.55% CH with a dosage regimen of one drop per eye every one to two hours during the waking day. There are reports of patients receiving corneal transplants to treat intractable photophobia and blepharospasm, band keratopathy, or corneal neovascularization.[4,5] However, cystine crystal deposition may recur in the corneal graft and corneal transplants are not intended to treat corneal cystine crystal deposits.[4,5]

Although patient input regarding treatment of CCCDs was not available for this review, the clinical experts consulted by CADTH identified the following limitations with pharmacy-compounded topical medications: poor access to the medications, lack of stability of the preparations and necessity for refrigeration at all times, short shelf life, and the need for frequent instillation of eye drops.

Drug

Cystadrops is indicated for the treatment of CCCDs in adults and children from two years of age with cystinosis. Cysteamine reduces corneal cystine crystal accumulation acting as a cystine-depleting agent by converting cystine to cysteine and cysteine-cysteamine mixed disulfides.[6] Cystadrops is a viscous topical ophthalmic solution containing 3.8 mg/mL cysteamine (0.55% CH). The Health Canada–recommended dosage is one drop in each eye, four times a day during waking hours.[6] The dose could be decreased progressively (to a minimum total daily dose of one drop in each eye) depending on the results of ophthalmic examination (such as CCCD, photophobia).[6] Key characteristics of Cystadrops are provided in Table 2.

Table 2: Key Characteristics of Cystadrops

	Cysteamine 3.8 mg/mL Ophthalmic Solution (Cystadrops)
Mechanism of Action	Cysteamine reduces corneal cystine crystal accumulation acting as a cystine-depleting agent by converting cystine to cysteine and cysteine-cysteamine mixed disulfides.
Indication[a]	Treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis
Route of Administration	Ophthalmic
Recommended Dose	One drop in each eye, 4 times a day during waking hours. The recommended interval between each instillation is 4 hours. The dose could be decreased progressively (to a minimum total daily dose of 1 drop in each eye) depending on the results of ophthalmic examination (such as corneal cystine crystal deposits, photophobia).
Serious Side Effects / Safety Issues	Contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
Other	• Temporary (less than 1 minute on average) blurred vision or other visual disturbances may affect the ability to drive or use machines. • Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Monitoring is required.

Source: Product monograph for Cystadrops.[6]

[a] Health Canada indication.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of cysteamine 3.8 mg/mL ophthalmic solution (Cystadrops) for the treatment of CCCD in adults and children from two years of age with cystinosis.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adults and children from 2 years of age with cystinosis. **Subgroups:** • Baseline corneal cystine crystal burden • Age • Cystinosis type (nephropathic infantile, nephropathic juvenile, and non-nephropathic)
Intervention	Cysteamine 3.8 mg/mL ophthalmic solution (Cystadrops) in accordance with the Health Canada–recommended dosage[a]
Comparators	• Placebo • Any other cysteamine ophthalmic solution
Outcomes	**Efficacy outcomes:** • Corneal cystine crystal burden • Ocular symptoms related to corneal cystine crystal deposits (e.g., photophobia, blepharospasm, and ocular discomfort or pain) • Vision-related function (e.g., visual acuity and contrast sensitivity) • Complications of corneal cystine crystal deposits (e.g., band keratopathy, corneal vascularization, filamentary keratitis, corneal erosion, and closed-angle glaucoma) • Health-related QoL • Need for corneal graft • Patient satisfaction with treatment • Caregiver burden **Harms outcomes:** • AEs, SAEs, WDAEs, mortality • Notable harms: ocular pain, redness, or stinging, blurred vision, and corneal endothelial damage
Study Design	Published and unpublished Phase III and IV RCTs

AE = adverse event; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Health Canada–recommended dosage is one drop in each eye, four times a day during waking hours. The dose could be decreased progressively (to a minimum total daily dose of one drop in each eye) depending on the results of ophthalmic examination.

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 All (1946-) through Ovid; Embase (1974-) through 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 Cystadrops (cysteamine) and cystinosis.

No filters were applied to limit the 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 3 for the detailed search strategies.

The initial search was completed on January 14, 2019. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on May 15, 2019. 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/resources/finding-evidence/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trial Registries, Databases (free), Internet Search, and Background. 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 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. Included studies are presented in

Table 4; excluded studies (with reasons) are presented in Appendix 4.

Results

Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in

Table 4. A list of excluded studies is presented in Appendix 4.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

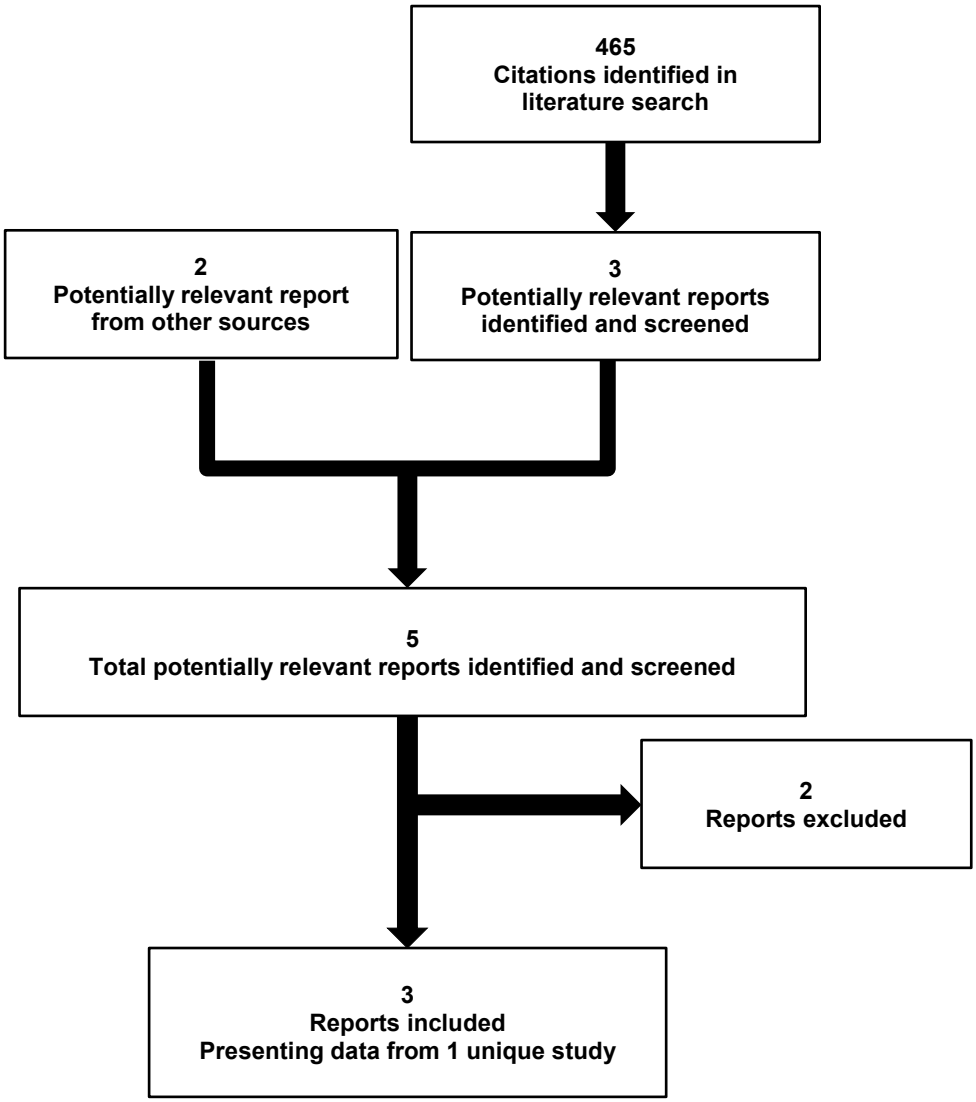


Table 4: Details of Included Study

		CHOC
Designs and Populations	**Study Design**	OL, parallel group, phase III RCT
	Locations	Two centres in France
	Randomized (N)	32
	Inclusion Criteria	• Diagnosis of cystinosis based on previous WBC cystine concentration > 1.5 nmol half-cystine per mg protein • Presence of corneal crystal deposits by slit-lamp exam within 3 months prior to inclusion • Ability to adhere to usual eye drops treatment • In the opinion of the investigator, patient will be adherent and has a high probability of completing the study
	Exclusion Criteria	• Uncontrolled hepatic disorder, cardiovascular disease, neurologic disease, or cancer • Hypersensitivity to cysteamine or excipients • Clinically significant (according to the investigator) laboratory tests out of normal range • History or presence of alcohol abuse or drug addiction • Age < 2 years • Patients likely to be non-compliant for study procedures or for whom a long-term follow-up seems difficult to achieve • Patients not undergoing IVCM were to be excluded from the primary end point analysis
Drugs	**Intervention**	1 drop of cysteamine 3.8 mg/mL (0.55% cysteamine hydrochloride) viscous solution (Cystadrops) in each eye 4 times a day (8:00 a.m., 12:00 a.m., 4:00 p.m., and 8:00 p.m.)
	Comparator(s)	1 drop of cysteamine (0.10% cysteamine hydrochloride) solution in each eye 4 times a day (8:00 a.m., 12:00 a.m., 4:00 p.m., and 8:00 p.m.)
Duration	**Phase**	
	Run-in	NA
	Treatment	90 days
	Follow-up	NA
Outcomes	**Primary End Point**	Change in IVCM total score from baseline to day 90
	Other End Points	• Change in IVCM individual corneal layer scores from baseline to day 90 • Photophobia graded on a 6-point scale by the investigator • Photophobia graded on a 6-point scale by the patient • Corneal cystine crystal score by slit-lamp examination from 0.00 to 3.00 in 0.25 increments • Corneal cystine crystal layer thickness by OCT • AEs, SAEs • Local adverse drug reactions (redness, blurring, itching, stinging, and burning) following each instillation • Visual acuity using the logMAR scale • Visual contrast sensitivity • Corneal staining with fluorescein • Intraocular pressure
Notes	**Publications**	Liang et al., 2017[12]

Source: Clinical Study Report and published report for the CHOC study.[7,12]

AE = adverse event; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; COMTOL = Comparison of Ophthalmic Medications for Tolerability; IVCM = in vivo confocal microscopy; logMAR = logarithm of the minimum angle of resolution; nmol = nanomole; NA = not applicable; OCT = optical coherence tomography; OL = open label; RCT = randomized controlled trial; SAE = serious adverse event; WBC = white blood cell.

Note: Aside from the published report, two additional reports were included (a clinical study report and an EMA assessment report).[7,13]

Included Studies

Description of Studies

One open-label (OL), parallel group phase III randomized controlled trial (RCT) was included. The Cysteamine Hydrochloride for nephrOpathic Cystinosis (CHOC) study (N = 32, conducted in 2013 at two centres in France by Orphan Europe SARL [part of the Recordati Group]) randomized patients (1:1) to one of two cysteamine hydrochloride ophthalmic solutions: a viscous cysteamine 3.8 mg/mL (equivalent to cysteamine hydrochloride [CH] 0.55%) solution (Cystadrops) and a CH 0.10% solution. Patients received study treatment for 90 days, with study visits at day 30 and day 90 and no screening or follow-up period. The objective of the CHOC study was to study the efficacy and safety of CH 0.55% versus CH 0.10% in patients with nephropathic cystinosis.

Populations

Inclusion and Exclusion Criteria

Included patients had a diagnosis of cystinosis by white blood cell cystine concentration (greater than 1.5 nanomoles of half-cystine per mg protein). Within the three months before the study, patients had to have corneal crystal deposits demonstrated by slit-lamp examination. Investigators only included patients who they judged would be compliant and likely to complete the study.

Patients were excluded if they were younger than two years of age or had significant disease, hypersensitivity to cysteamine or any excipients in the study drugs, a history or presence of alcohol or substance use problems, or clinically significant laboratory tests outside of the normal range. Patients likely to be non-compliant with regard to study procedures or for whom a long-term follow-up would have been difficult were excluded. Patients who did not undergo the in vivo confocal microscopy (IVCM) procedure at baseline were excluded from the analysis of the primary end point. It was expected that IVCM might not be feasible in younger children.

Baseline Characteristics

All patients had been diagnosed with infantile nephropathic cystinosis at age 46 months or younger, except for one patient in the CH 0.55% group who was diagnosed with late-onset nephropathic cystinosis at 30 years of age. Pediatric patients made up 53.3% of the CH 0.55% group and 68.8% of the CH 0.10% group. All adult patients and most pediatric patients underwent IVCM at baseline and could therefore be evaluated for the primary end point. There were wide ranges of disease duration in both groups (0.8 to 33.9 years and 0.7 to 35.5 years in the CH 0.55% and CH 0.10% group, respectively), though mean duration was similar between the groups (15.9 and13.8 years).

All patients had previously used topical cysteamine, with mean durations of treatment of [redacted] in the CH 0.55% group and [redacted] in the CH 0.10% group. [redacted] were taking systemic cysteamine.

One patient in the CH 0.10% group had a corneal transplant 11 days before the start of study treatment. One patient in each group had a history of corneal neovascularization.

While mean IVCM total score was similar between the groups at baseline (10.6 in the CH 0.55% group and 10.8 in the CH 0.10% group), the CH 0.55% group on average had a greater corneal cystine crystal burden than the CH 0.10% group by other measures (2.26

versus 1.98 for CCCS and 275 µm versus 260 µm for corneal cystine crystal layer thickness measured by optical coherence tomography). The CH 0.55% group also had higher mean photophobia scores (indicating worse photophobia), compared with the CH 0.10% group (1.73 versus 1.61 for patient-assessed photophobia and 1.87 versus 1.68 for investigator-assessed photophobia). Patient-assessed photophobia score was 0 (no photophobia) at baseline in six of 30 eyes (20% of eyes) in the CH 0.55% group and eight of 32 eyes (26%) in the CH 0.10% group. Investigator-assessed photophobia score was 0 (no photophobia) in four eyes (13%) at baseline in each treatment group.

Table 5: Summary of Baseline Characteristics

Title	CHOC	
	CH 0.55% N = 15 FAS	**CH 0.10% N = 16 FAS**
Male, n (%)	7 (46.7)	8 (50.0)
Female, n (%)	8 (53.3)	8 (50.0)
Age, years		
Mean (SD)	19.2 (15.5)	15.1 (10.3)
Median (range)	13.5 (2.87, 62.6)	11.8 (3.49, 36.0)
Age category, n (%)		
< 12 years	5 (33.3)	8 (50.0)
12 to 17 years	3 (20.0)	3 (18.8)
≥ 18 years	7 (46.7)	5 (31.3)
IVCM and age stratum, n (%)		
No IVCM	4 (26.7)	5 (31.1)
IVCM and < 12 years	2 (13.3)	4 (25.0)
IVCM and 12 to 17 years	2 (13.3)	2 (12.5)
IVCM and ≥ 18 years	7 (46.7)	5 (31.3)
Disease duration, years		
Mean (SD)	15.9 (11.0)	13.8 (10.8)
Median (range)	12.7 (0.775, 33.9)	9.20 (0.695, 35.5)
Age at diagnosis, months		
Mean (SD)	38.4 (89.3)	15.5 (11.1)
Median (range)	16.0 (5.0, 360)	15.5 (5.0, 46.0)
Previous renal transplantation, n (%)	[redacted]	[redacted]
Mean age at renal transplantation (SD), years	[redacted]	[redacted]
Mean WBC cystine (SD), nmol ½ cystine per mg of protein	[redacted]	[redacted]
Duration of previous topical cysteamine, months		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Systemic cysteamine use, n (%)	[redacted]	[redacted]
RP103 (Procysbi) use	[redacted]	[redacted]
Cystagon use	[redacted]	[redacted]
Duration of previous systemic cysteamine treatment, months	N = 13	N = 15
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Previous corneal transplant, n (%)	[redacted]	[redacted]
History of eye disorders, n (%)	[redacted]	[redacted]

Title	CHOC	
Corneal neovascularization	[redacted]	[redacted]
Strabismus	[redacted]	[redacted]
Amblyopia	[redacted]	[redacted]
Eye irritation	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]
Ocular hyperemia	[redacted]	[redacted]
Optic nerve cupping	[redacted]	[redacted]
Median number of previous treatments (IQR)	[redacted]	[redacted]
IVCM total score	N = 20 eyes	N = 20 eyes
Mean (SD)	10.6 (4.18)	10.8 (3.47)
Median (range)	10.9 (3.20, 19.0)	10.8 (4.17, 16.2)
Photophobia score by patient	N = 30 eyes	N = 31 eyes
Mean (SD)	1.73 (1.31)	1.61 (1.23)
Median (range)	2.00 (0.00, 4.00)	2.00 (0.00, 4.00)
Photophobia score by investigator	N = 30 eyes	N = 31 eyes
Mean (SD)	1.87 (1.17)	1.68 (1.05)
Median (range)	2.00 (0.00, 4.00)	2.00 (0.00, 4.00)
Corneal cystine crystal score	N = 30 eyes	N = 31 eyes
Mean (SD)	2.26 (0.563)	1.98 (0.500)
Median (range)	2.25 (1.50, 3.00)	2.00 (1.00, 3.00)
Corneal cystine crystal layer thickness by OCT, µm	N = 30 eyes	N = 29 eyes
Mean (SD)	275 (159)	260 (167)
Median (range)	245 (46.0, 580)	180 (42.0, 558)

Source: Clinical study report for the CHOC study.[7]

CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; FAS = full analysis set; IQR = interquartile range; IVCM = in vivo confocal microscopy; OCT = optical coherence tomography; SD = standard deviation; WBC = white blood cell.

NOTE: N refers to number of patients unless otherwise specified.

Interventions

Patients were randomized following baseline ophthalmologic assessments using an interactive voice or Web response system and a randomization list produced by the interactive response system provider. Randomization was stratified based on whether IVCM was performed and age category (11 years or less, 12 to 17 years, and at least 18 years). There was no effort to blind patients or investigators to treatment assignment. The rationale provided was that the viscosities of the two study medications differed.

The investigational product was a viscous ophthalmic solution with 3.8 mg/mL of cysteamine (0.55% CH by weight) and the control drug was an ophthalmic solution with 0.10% CH supplied by Agence Générale des Equipements et Produits de Santé, l'Assistance Publique – Hôpitaux de Paris Hospital Pharmacies. After dispensing, the vials were to be stored between 2°C and 8°C and could be used for seven consecutive days. The CH 0.55% solution had the following excipients: disodium edetate, benzalkonium chloride, carmellose sodium, citric acid monohydrate, sodium hydroxide, hydrochloric acid, and water for injection. The CH 0.10% solution had the following excipients: benzalkonium chloride, ascorbic acid, hydrochloric acid, dextran 40, and sodium chloride.

In both treatment groups, patients were to administer one drop of solution in each eye four times daily at approximately 8:00 a.m., 12:00 a.m., 4:00 p.m., and 8:00 p.m. The treatment period was 90 days.

There were no required or prohibited concomitant medications during the study. Other ophthalmic formulations were allowed, but they could not be administered within 10 minutes of study drug instillation. Details on concomitant ophthalmological medications are provided in Table 6. No patients were on concomitant ophthalmic CH medications and the most common categories of concomitant ophthalmic medications were anti-infectives ([redacted] in the CH 0.10% group and [redacted] in the CH 0.55% group), anti-inflammatory agents ([redacted] in the CH 0.55% and CH 0.10% groups, respectively), and other agents (particularly [redacted]). While all included patients had a history of using topical cysteamine, it was not specified whether all patients had been using topical cysteamine up to the start of the trial.

Patients (or parents) were to record adherence to study medication in a diary four times daily. The investigator and pharmacist accounted for used and unused study medication in drug administration records. Patient diaries were provided at baseline and at day 30. Adherence was determined based on the diaries that were filled out and returned by patients. If neither diary was returned, the value was reported as missing.

Table 6: Concomitant Ophthalmological Medications

	CHOC	
	CH 0.55% N = 15 FAS	CH 0.10% N = 16 FAS
Anti-infectives	[redacted]	[redacted]
Fusidic acid	[redacted]	[redacted]
Tobramycin	[redacted]	[redacted]
Dacryoserum	[redacted]	[redacted]
Dacudoses	[redacted]	[redacted]
Anti-inflammatory agents	[redacted]	[redacted]
Indomethacin	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]
Combination anti-inflammatory agents and anti-infectives	[redacted]	[redacted]
Tobradex	[redacted]	[redacted]
Decongestants and anti-allergics	[redacted]	[redacted]
Cromoglicate sodium	[redacted]	[redacted]
Levocabastine hydrochloride	[redacted]	[redacted]
Spaglumic acid	[redacted]	[redacted]
Other	[redacted]	[redacted]
Carmellose	[redacted]	[redacted]
Carmellose sodium	[redacted]	[redacted]
Retinol	[redacted]	[redacted]
Sodium chloride	[redacted]	[redacted]
Ciclosporin	[redacted]	[redacted]

Source: Clinical study report for the CHOC study.[7]

CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; FAS = full analysis set.

NOTE: N refers to number of patients.

Efficacy Outcomes

Corneal Cystine Crystal Burden

In vivo confocal microscopy total score (primary end point)

The primary end point was the change from baseline to day 90 in IVCM total score. IVCM is a non-invasive technique used to assess cellular-level changes in the cornea using a laser scanning confocal microscope. IVCM was performed by the investigator using the Rostock Cornea Module of the Heidelberg Retina Tomograph at baseline, day 30, and day 90. A drop of topical anesthetic (oxybuprocaine 0.4%) and a drop of gel tear substitute (carbomer 0.2%) were administered to the lower conjunctival fornix. Crystal density was rated in the central cornea (0.4 mm × 0.4 mm field of view) of each eye on an ordinal scale of 0 to 4 (0 = no crystals; 1 = less than 25% of deposits in the images; 2 = 25% to 50% of deposits in the images; 3 = 50% to 75% of deposits in the images; 4 = 75% to 100% of deposits in the images) for each of the following seven corneal layers: epithelium, basal epithelium, Bowman's layer, superficial stroma, middle stroma, deep stroma, and endothelium. IVCM images were rated by a single reader who was blinded to treatment assignment. According to the European Medicines Agency's assessment report,[13] approximately 200 images in each eye were acquired, yielding approximately five to 10 images of good quality per layer per eye that could be rated. The score for each layer was the mean of the scores for all the images of that layer. The total score, ranging from 0 to 28, was produced by summing the scores for all seven layers. Higher scores indicated greater corneal crystal density and/or burden. However, there was limited evidence found for the validity of the IVCM total score and no evidence was found for its reliability or MCID. For more information on IVCM total score, see Appendix 6.

Corneal cystine crystal score

Corneal crystal deposits were also evaluated in each eye at baseline, day 30, and day 90 using slit-lamp examination and the corneal cystine crystal score (CCCS) defined in Gahl et al., 2000.[14] The CCCS was determined by the investigator in each eye with a possible range of 0.00 (clarity at the centre) to 3.00 (greatest recognizable crystal density) in increments of 0.25 using the reference slit-lamp photographs in the publication by Gahl et al.[14] There was limited evidence found for the validity of the CCCS and no evidence found for its reliability or MCID. For more information on CCCS, see Appendix 6.

Crystal layer thickness by optical coherence tomography

The thickness of the corneal crystal layer was measured using high-resolution optical coherence tomography (OCT) of the anterior segment. There was little evidence found for the validity of the corneal crystal layer thickness as measured by OCT and no evidence found for its reliability or MCID. For more information on this outcome, see Appendix 6.

Ocular Symptoms Related to Corneal Cystine Crystal Deposits

Photophobia

Photophobia was graded by both the investigator and the patients on an ordinal scale of 0 to 5. Higher scores correspond to worse or more severe photophobia. However, no evidence was found for the validity, reliability, or MCID of the photophobia scales. For more information on these scales, see Appendix 6.

The patient-rated photophobia scale was defined as follows:

- 0 = no photophobia, no discomfort (none)
- 1 = slight difficulty with light causing occasional eye blinking (trace)
- 2 = slight difficulty with light causing regular eye blinking (mild)
- 3 = moderate difficulty with light requiring the wearing of sunglasses (moderate)
- 4 = severe difficulty with light requiring the wearing sunglasses of in a quasi-permanent manner (severe)
- 5 = extreme difficulty with light requiring the patient to remain inside, cannot bear natural light even with sunglasses (extreme)

The investigator-rated photophobia scale was defined as follows:

- 0 = no photophobia (none)
- 1 = photophobia to light from indirect ophthalmoscope (trace)
- 2 = photophobia to light from slit-lamp beam (mild)
- 3 = photophobia to light from torch (moderate)
- 4 = photophobia needing dark glasses even indoors (severe)
- 5 = unable to open eyes even indoors (extreme)

Vision-Related Function

Visual acuity and contrast sensitivity were considered to be safety outcomes in the CHOC study.

Visual acuity

Visual acuity on the logarithm of the minimum angle of resolution (logMAR) scale was assessed. The type of chart used was not specified. A lower value corresponded to better visual acuity.

Visual contrast sensitivity

Visual contrast sensitivity was measured using a contrast sensitivity chart (type not specified) with values ranging from –0.3 to +0.3. A lower value corresponded to better contrast sensitivity.

Complications of Corneal Cystine Crystal Deposits

Corneal erosions and intraocular pressure (IOP) were considered to be safety outcomes in the CHOC study.

Corneal erosions

Corneal erosions were assessed using fluorescein staining during slit-lamp examination. Corneal staining was graded on a 5-point scale (0 = none; 1 = trace; 2 = mild; 3 = moderate; 4 = severe) for each segment (superior, inferior, nasal, temporal, central) and the individual scores were summed to yield a total score out of 20. Higher scores indicated greater damage to the corneal epithelium.

Intraocular pressure

IOP was measured using tonometry. Further details were not provided.

Health-Related Quality of Life

There were no outcomes available for health-related quality of life.

Need for CornealGgraft

There were no outcomes available for patient need of a corneal graft.

Patient Satisfaction With Treatment

The Comparison of Ophthalmic Medications for Tolerability questionnaire, an instrument developed for assessing the frequency and impact of common side effects of topical therapies for glaucoma, was presented to the adult patients at each time point. One question asked by the interviewer was, “Overall, how satisfied, if at all, have you been with the test medication you have been taking?” The six response options ranged from “totally satisfied” to “totally dissatisfied.”

Caregiver Burden

There were no outcomes available for caregiver burden.

Safety Outcomes

Adverse Events

AEs and serious AEs (SAEs) were recorded by study personnel in electronic case report forms according to standard medical terminology. AEs and SAEs were reported separately from LADRs lasting for less than one hour (see below). SAEs occurring up to 30 days following study completion were reported.

Notable Harms

Local adverse drug reactions

Patients (or parents) recorded the following information on specific LADRs following each instillation of study medication: time of instillation, the occurrence of local symptoms (redness, blurring, itching, stinging, and burning), whether local symptoms that occurred lasted for shorter than or longer than one hour, and the severity of each local symptom (1 = mild, 2 = moderate, 3 = severe, 4 = unbearable).

Statistical Analysis

The statistical analysis plan for the CHOC study was finalized following completion of the trial. All efficacy analyses were performed using the eye as the unit of analysis. Superiority testing of the primary end point, change in IVCM total score from baseline to day 90, was performed using a generalized estimating equation (GEE) model with a significance level of 0.05. The linear model included treatment group as a factor, baseline IVCM total score as a covariate, and each pair of eyes as repeated measurements within each patient. An autoregressive structure was used for the variance-covariance matrix. Results for the score test and robust standard errors were reported.

Change from baseline to day 90 for the other efficacy end points (CCCS, crystal layer thickness by OCT, and photophobia) was evaluated with analysis of covariance (ANCOVA) models with treatment group as a factor, baseline value as a covariate, and each pair of eyes as repeated measures within each patient. There was no adjustment for multiple end points and no imputation of missing data.

Sample size calculations for the primary end point were based on the previous open-label (OL), dose-response, phase I/IIa trial (OCT-1 study,[15,16] see Appendix 6 for details). Assuming no mean change in IVCM total score with CH 0.10% treatment, a mean reduction in IVCM total score of –3.0 points with CH 0.55% treatment, a SD in mean change in IVCM total score of 2.0, and a percentage of patients discontinuing of 10%, a sample size of 12 patients per treatment group was expected to have 90% power to establish superiority of CH 0.55% at a two-sided significance level of 0.05.

Analysis Populations

The full analysis (FA) set was defined as all randomized patients (or eyes) who received at least one dose of study treatment. The per-protocol (PP) set was defined as all patients (or eyes) in the FA set who did not have any major protocol deviations. The efficacy analyses were performed using the FA set with sensitivity analyses performed in the PP set. Safety analyses were based on the safety set, which included all patients who received at least one dose of study treatment and was identical to the FA set. In the analysis of the primary efficacy end point, only patients who were able to undergo the IVCM procedure were included in the FA and PP sets. Subgroup analyses were performed for all efficacy and safety outcomes by age group (less than and at least 18 years old).

Patient Disposition

Patient disposition is detailed in Table 7. One patient in the CH 0.10% group was lost to follow-up and no information on study treatment administration was available for this patient. Two patients in the CH 0.10% group could only be assessed with IVCM in one eye, due to amblyopia in one patient and previous corneal transplant surgery in the other patient. The numbers of patients who underwent IVCM assessment at baseline were similar between treatment groups in both the FA and PP populations.

Due to major protocol violations, three patients in the CH 0.55% group and six patients in the CH 0.10% group were excluded from the PP population.

Table 7: Patient Disposition

	CHOC	
	CH 0.55%	CH 0.10%
Included, N	32	
Randomized, N	15	17
Discontinued, N (%)	0	1 (5.9)[a]
FAS, N	15	16
FAS/IVCM, N	11	11
PP, N	12	11
PP/IVCM, N	9	8
Safety, N	15	16

Source: Clinical study report for the CHOC study.[7]

CH = cysteamine hydrochloride; CHOC = cysteamine hydrochloride for nephropathic cystinosis; FAS = full analysis set; IVCM = in vivo confocal microscopy; PP = per-protocol.

NOTE: IVCM refers to patients who had an IVCM assessment prior to the study.

NOTE: N refers to number of patients.

[a] Patient was lost to follow-up after randomization.

Exposure to Study Treatments

One patient in the CH 0.55% group discontinued treatment on day 86 without restarting treatment due to allergic conjunctivitis. One patient in each group temporarily discontinued treatment due to an AE, one in the CH 0.55% group due to dizziness following crystal detachment in the inner ear and one in the CH 0.10% group due to corneal graft rejection in one eye (with treatment restarted in the other eye only).

Duration of treatment, number of instillations, and adherence were greater in the CH 0.10% group than in the CH 0.55% group (Table 8). Although the mean number of days of interruption was greater in the CH 0.55% group ([redacted]), adherence ignoring days of interruption was still lower in the CH 0.55% group than in the CH 0.10% group (mean of [redacted] and median of [redacted]).

Table 8: Treatment Exposure

	CHOC	
	CH 0.55% N = 15 FAS	CH 0.10% N = 16 FAS
Duration of treatment intake, days		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Number of days of treatment intake		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Total number of instillations		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Number of days of interruption		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

	CHOC	
Overall adherence including days of interruption, %	N = 14	N = 16
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Overall adherence during days of treatment intake only, %	N = 14	N = 16
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

Source: Clinical study report for the CHOC study.[7]

CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; FAS = full analysis set; SD = standard deviation.

NOTE: N refers to number of patients.

Major and minor protocol deviations were defined and identified during the data review meeting prior to database lock. There was no mention of a blinded data review. All major protocol deviations (Table 9) were related to treatment adherence outside of a certain window or treatment interruptions of at least one week. A higher percentage of patients in the CH 0.10% group than in the CH 0.55% group had major protocol deviations ([redacted]). [redacted] patients in the CH 0.10% group and [redacted] in the CH 0.55% group received over 120% of the planned instillations while [redacted] patients in each group received less than 80% of the planned instillations (one in the CH 0.10% group being lost to follow-up).

Table 9: Major Protocol Deviations

	CHOC	
	CH 0.55% N = 15 Randomized	**CH 0.10% N = 17 Randomized**
Patients with ≥ 1 major protocol deviation, n (%)	[redacted]	[redacted]
Patients with < 80% adherence during days of treatment intake, n (%)	[redacted]	[redacted]
Patients with > 120% adherence during days of treatment intake, n (%)	[redacted]	[redacted]
Patients with < 80% adherence including days of interruption, n (%)	[redacted]	[redacted]
Patients with > 120% adherence including days of interruption, n (%)	[redacted]	[redacted]
Patients with treatment interruption ≥ 1 week, n (%)	[redacted]	[redacted]

Source: Clinical study report for the CHOC study.[7]

CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study.

NOTE: N refers to number of patients.

NOTE: Adherence was based on patient diary card data.

[a] One patient in the CH 0.10% group was lost to follow-up and no information on study treatment administration was available for this patient.

Critical Appraisal

Internal Validity

In terms of imbalances between treatment groups at baseline, mean baseline CCCS, patient-assessed and clinician-assessed photophobia scores, and corneal crystal layer thickness by OCT were worse in the CH 0.55% group. It is unknown if these factors could have led to bias in favour of CH 0.55% (e.g., if a larger crystal burden meant greater potential for improvement).

According to both photophobia scales, there were eyes in both treatment groups with no photophobia at baseline. A reduction (improvement) in photophobia score would not have been possible these eyes.

Treatment adherence ranged widely within each group during the duration of the treatment period. In the CH 0.55% group, patients did not go above the planned number of instillations while [redacted] patients in the CH 0.10% group administered over 120% of the planned instillations. [redacted] patients in each group had less than 80% treatment adherence. Overall adherence was greater in the CH 0.10% group and it appears that any bias in efficacy arising from differences in treatment exposure would likely have been against CH 0.55%. Sensitivity analysis in the PP set is helpful for confirming the results of the primary analysis in the subset of patients with good treatment adherence. For AEs and LADRs, there could have been a bias from differences in treatment exposure in favour of CH 0.55%.

Due to the lack of blinding to treatment assignment for both patients and investigators, there was potential for bias in patient-assessed outcomes such as patient-rated photophobia, treatment adherence, LADRs, and AEs, as well as outcomes that relied on the investigator's subjective judgment (particularly CCCS and investigator-rated photophobia). Although IVCM images were graded by a blinded reviewer, the images were acquired by the unblinded investigators. According to the clinical experts consulted for this review, there was a potential for bias in IVCM scores since crystal density can vary with position across the cornea and with depth within each corneal layer. By adjusting the position of the tomograph over the cornea or selecting particular images within a given layer, the investigator could have influenced the individual scores.

The validity, reliability, and MCID of the patient- and investigator-rated photophobia scales are unknown. It is also unknown how patient-rated photophobia was assessed in young children who were incapable doing self-report. The clinical experts consulted for this review found both scales to have some degree of subjectivity. As well, the experts did not consider the light sources and settings defined in the investigator-rated photophobia scale to be standardized and they could vary in intensity depending on the investigator. For example, an investigator could easily modulate severity of photophobia according to the scale by adjusting the slit-lamp beam intensity. Finally, there was no information on how photophobia as assessed on these scales impacted patients' function, activities, or quality of life. As noted by the clinical experts, patients may be affected by photophobia differently based on their resilience.

IVCM total score showed a moderate correlation with an unvalidated patient-rated photophobia scale[17] and its reliability and MCID are unknown. As the European Medicines Agency (EMA) noted in their assessment report for Cystadrops,[13] the use of equal weighting for each corneal tissue layer to derive the total score was not justified. CCCS showed a weak correlation with an unvalidated patient-rated photophobia scale,[17] and its reliability and MCID are unknown. Corneal cystine crystal layer thickness measured with OCT was moderately correlated with an unvalidated patient-rated photophobia scale,[17] with unknown reliability and MCID.

Outcomes related to corneal complications (corneal staining and IOP) and visual function (visual acuity and contrast sensitivity) were considered to be safety outcomes in the trial and statistical analyses were not performed on them. Methodological details for these outcomes were scant as the tonometer used to measure IOP and the charts used to measure acuity and contrast sensitivity were not specified. The clinical experts consulted for this review were not aware of any evidence for the validity of the corneal staining scale. The experts noted that IOP varies throughout the day and it is not clear if IOP was measured at the same time of day for all patients.

The version history of the statistical analysis plan indicates that changes to the plan were made based on data review meeting discussions and there was no indication in the clinical study report that the data review was conducted in a blinded manner. Therefore, one cannot rule out the possibility that the choice of statistical methods was influenced by the study data and constituted a risk of selective reporting bias.

A true intention-to-treat (ITT) analysis was not performed as one patient discontinued the study and was not included in the FA set. In addition, there was no sensitivity analysis of the potential effects of missing data.

The models for statistical analysis were appropriate and were adjusted for baseline value and within-patient correlation between eyes. However, there was no rationale given for the choice of model types or the use of a GEE model for the primary end point and ANCOVA models for the other efficacy end points. There was no control for multiplicity of outcomes and outcomes aside from the primary end point are at risk of an inflated type I error rate. Overall, the study was limited by its small sample size for many other clinically meaningful outcomes. Statistical analyses beyond descriptive statistics were not planned for the outcomes related to visual function and complications of CCCD.

External Validity

Study Population

Based on the baseline characteristics of the CHOC study population, the clinical experts consulted for this review found that the patients were representative of Canadian patients with cystinosis. Also, the experts considered the results to be generalizable to the entire cystinosis population as opposed to only those with nephropathic cystinosis.

The trial only included patients who, in the opinion of the investigator, were likely to adhere to the treatment regimen and complete the study. Therefore, treatment adherence in the study may have been better than would be observed in the cystinosis patient population as a whole. Also, patients may be more likely to adhere to the full dosage regimen while participating in a clinical trial as opposed to outside of a trial.

The treatment regimen in the control arm was not representative of treatment received by Canadian patients with cystinosis for corneal crystal buildup. According to the clinical experts consulted for this review, the CH 0.10% regimen of four instillations daily would not be expected to result in an improvement in symptoms such as photophobia. This is in contrast to pharmacy-compounded CH eye drops in Canada that are typically of a higher concentration than 0.1%, and are administered every one to two hours during the day. The EMA noted in their assessment report that CH 0.10% instilled four times a day would not be expected to effectively decrease corneal crystal burden.[13]

Since treatment adherence could determine the effectiveness of the intervention and adherence may be difficult to maintain over the longer-term, a treatment duration of longer than 90 days is needed to assess whether any benefits of treatment are maintained. For lifelong treatment of a progressive and detrimental disease, it is important to assess the long-term efficacy and safety as well as whether the observed beneficial effect is sustained and whether side effects can become more frequent and severe over time. While a 90-day treatment period may be sufficient to observing a change in photophobia or visual function due to treatment, the clinical experts consulted for this review noted that a longer follow-up period for the efficacy outcomes would have been more informative regarding the comparative efficacy and safety of CH 0.55% versus CH 0.10%.

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported below.

Corneal Cystine Crystal Burden

In Vivo Confocal Microscopy Score (Primary End Point)

The primary end point analysis showed that CH 0.55% was statistically significantly superior to CH 0.10% in reducing overall corneal cystine crystal burden as measured by IVCM total score (difference in mean change from baseline of –3.84 [95% CI, –5.58 to –2.11]; $P < 0.0001$). Detailed results are provided in Table 10. Results in the set were consistent with the main analysis in the FA set. Subgroup analyses in the pediatric and adult populations suggested similar changes in IVCM total score in both populations. Subgroup analyses by baseline corneal cystine crystal burden or cystinosis type were not available for any of the outcomes.

Mean IVCM scores for each individual corneal layer are summarized per treatment group in Table 18 in Appendix 5. Baseline IVCM scores for the epithelium and basal epithelium ranged from 0.822 to 1.40, while baseline IVCM scores for Bowman's layer and the superficial, medium, and deep stroma ranged from 1.42 to 3.20. Presence of corneal cystine crystals on IVCM in the endothelium was negligible. The decrease in mean IVCM score from baseline to day 90 was numerically greater in the 0.55% group than in the 0.10% group for each layer (Table 18).

The FA population for IVCM consisted of both eyes in all patients who underwent IVCM at baseline and excluded one eye in two patients in the CH 0.10% group due to amblyopia and previous corneal transplant surgery. Within this set of patients, IVCM data were missing for one patient at baseline in the CH 0.55% group and was missing in one patient and one eye in a second patient at day 90 in the CH 0.10% group.

Corneal Cystine Crystal Score

Mean CCCS, assessed using slit-lamp examination with a possible range of 0 to 3, decreased (improved) from baseline to day 90 in the CH 0.55% group and not in the CH 0.10% (mean change of –0.592 [SD of 0.523] versus 0.105 [SD of 0.240]; Table 10). There was no control for multiple outcomes and statistically significant results outside of the primary end point must be interpreted with this in mind. The results in the PP set were consistent with those in the FA set. Similar trends were observed in the pediatric and adult subgroups as in the entire FA population (Table 16 and Table 17).

Crystal Layer Thickness By Optical Coherence Tomography

The mean thickness of the corneal cystine crystal layer, assessed by OCT, decreased (improved) from baseline to day 90 in the CH 0.55% group and not in the CH 0.10% group (mean change of –46.3 µm [SD of 55.3 µm] versus 10.6 µm [SD of 43.6 µm]; Table 10). The results in the PP set were consistent with those in the FA set. Similar trends were observed in the pediatric and adult subgroups as in the entire FA population (Table 16 and Table 17).

Table 10: Corneal Cystine Crystal Burden

	CHOC	
	CH 0.55% FAS	**CH 0.10% FAS**
IVCM total score (primary end point)	N = 22 eyes	N = 20 eyes
Mean at baseline (SD)	10.6 (4.18) N = 20[a]	10.8 (3.47) N = 20
Mean at day 90 (SD)	6.04 (2.08) N = 20[a]	9.81 (3.81) N = 17[a]
Mean change (SD)	–4.60 (3.12) N = 20[a]	–0.455 (3.38) N = 17[a]
Difference in mean change, CH 0.55% vs. CH 0.10% (95% CI)	–3.84 (–5.58, –2.11)	
P value	< 0.0001	
IVCM total score, pediatric subgroup	N = 8 eyes	N = 12 eyes
Mean at baseline (SD)	10.1 (3.93)	9.60 (3.33)
Mean at day 90 (SD)	6.12 (1.54)	9.02 (3.74) N = 11
Mean change (SD)	–4.03 (2.95)	–0.485 (3.49) N = 11
P value	NR[b]	
IVCM total score, adult subgroup	N = 14 eyes	N = 8 eyes
Mean at baseline (SD)	11.0 (4.48) N = 12	12.6 (3.02)
Mean at day 90 (SD)	5.99 (2.44) N = 12	11.3 (3.84) N = 6
Mean change (SD)	–4.98 (3.29) N = 12	–0.400 (3.51) N = 6
Difference in mean change, CH 0.55% vs. CH 0.10% (95% CI)	–5.09 (–7.42, –2.77)	
P value	< 0.0001[c]	
Corneal cystine crystal score	N = 30 eyes	N = 32 eyes
Mean at baseline (SD)	2.26 (0.563) N = 30	1.98 (0.500) N = 31
Mean at day 90 (SD)	1.67 (0.729) N = 30	2.09 (0.519) N = 31
Mean change (SD)	–0.592 (0.523) N = 30	0.105 (0.240) N = 31
P value	0.0015[c]	
Crystal layer thickness by OCT, µm	N = 30 eyes	N = 32 eyes
Mean at baseline (SD)	275 (159) N = 30	260 (167) N = 29
Mean at day 90 (SD)	241 (133) N = 28	259 (174) N = 32
Mean change (SD)	–46.3 (55.3) N = 28	10.6 (43.6) N = 29

	CHOC
P value	0.0031[c]

Source: Clinical study report for the CHOC study.[7]

Abbreviations: CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; CI = confidence interval; FAS = full analysis set; IVCM = in vivo confocal microscopy; OCT = optical coherence tomography; SD = standard deviation.

NOTE: N refers to number of eyes.

NOTE: Each pair of eyes was considered as repeated measurements within each patient.

NOTE: For IVCM total score, a generalized estimating equation model was used which included treatment group as a factor and baseline IVCM total score as a covariate. For all other efficacy end points, an analysis of covariance model was used which included treatment group as a factor and baseline value as a covariate.

[a] IVCM data were missing for one patient at baseline in the CH 0.55% group in addition to one patient and one eye in second patient at day 90 in the CH 0.10% group.

[b] Model did not converge.

[c] *P* value is provided for descriptive purposes only as there was no control for multiple outcomes.

Ocular symptoms related to corneal cystine crystal deposits

Patient-Rated Photophobia

Mean photophobia rated by the patient on a scale of 0 to 5 decreased (improved) in the CH 0.55% group (mean change of –0.267 [SD of 0.583]) and numerically worsened in the CH 0.10% group (mean change of 0.226 [SD of 0.717]; (Table 11). The results in the PP set followed the same trends as in the FA set. Similar trends were observed in the pediatric and adult subgroups as in the entire FA population (Table 16 and Table 17).

In both treatment groups, most patients experienced no change in self-rated photophobia from baseline to day 90. Higher percentages of eyes in the CH 0.55% group versus the CH 0.10% group had an improvement of 1 point ([redacted]) and 2 points ([redacted]; Table 11). There was a worsening in 25.8% of eyes in the CH 0.10% group and none in the CH 0.55% group.

Investigator-Rated Photophobia

Mean photophobia rated by the investigator on a scale of 0 to 5 decreased (improved) in the CH 0.55% group (mean change of –0.633 [SD of 0.765]) and did not change appreciably in the CH 0.10% group (mean change of 0.065 [SD of 0.442]; (Table 11. The results in the PP set followed the same trends as in the FA set. Similar trends were observed in the pediatric and adult subgroups as in the entire FA population (Table 16 and Table 17).

The same trends with respect to individual response were observed with investigator-rated photophobia as with patient-rated photophobia, with numerically greater percentages of eyes in the CH 0.55% group having an improvement and greater percentages of eyes in the 0.10% group having a worsening (Table 11).

Table 11: Photophobia

	CHOC	
	CH 0.55% FAS	**CH 0.10% FAS**
Photophobia rated by patient	N = 30 eyes	N = 32 eyes
Mean at baseline (SD)	1.73 (1.31) N = 30	1.61 (1.23) N = 31
Mean at day 90 (SD)	1.47 (1.17) N = 30	1.84 (1.27) N = 32
Mean change (SD)	–0.267 (0.583) N = 30	0.226 (0.717) N = 31
P value	NR[a]	
Change category from baseline to day 90, n (%)	N = 30 eyes	N = 31 eyes
Improved by 2 points	[redacted]	[redacted]
Improved by 1 point	[redacted]	[redacted]
No change	[redacted]	[redacted]
Worsened by 1 point	[redacted]	[redacted]
Worsened by 2 points	[redacted]	[redacted]
Photophobia rated by investigator	N = 30 eyes	N = 32 eyes
Mean at baseline (SD)	1.87 (1.17) N = 30	1.68 (1.05) N = 31
Mean at day 90 (SD)	1.23 (1.17) N = 30	1.81 (1.20) N = 32
Mean change (SD)	–0.633 (0.765) N = 30	0.065 (0.442) N = 31
P value	0.0048[b]	
Change category from baseline to day 90, n (%)	N = 30 eyes	N = 31 eyes
Improved by 2 points	[redacted]	[redacted]
Improved by 1 point	[redacted]	[redacted]
No change	[redacted]	[redacted]
Worsened by 1 point	[redacted]	[redacted]

Source: Clinical study report for the CHOC study.[7]

CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; FAS = full analysis set; NR = not reported; SD = standard deviation.

NOTE: N refers to number of eyes.

NOTE: Unit of analysis was the eye and each pair of eyes was considered as repeated measurements within each patient.

NOTE: An analysis of covariance model was used which included treatment group as a factor and baseline score as a covariate.

[a] Model did not converge.

[b] *P* value is provided for descriptive purposes only as there was no control for multiple outcomes.

Vision-Related Function

The CH 0.55% group had worse visual acuity and contrast sensitivity on average at baseline and experienced a greater decrease (improvement) in both outcomes than the CH 0.10% group (Table 12). Statistical analyses were not performed and there was a substantial amount of missing data in the CH 0.55% group for both outcomes.

Table 12: Vision-Related Function

	CHOC	
	CH 0.55% Safety Set N = 30 eyes	**CH 0.10% Safety Set N = 32 eyes**
Visual acuity in LogMAR scale		
Mean at baseline (SD)	0.236 (0.362) N = 22	0.161 (0.298) N = 29
Mean at day 90 (SD)	0.138 (0.389) N = 22	0.106 (0.280) N = 30
Mean change (SD)	–0.098 (0.151) N = 22	–0.069 (0.146) N = 29
Visual contrast sensitivity		
Mean at baseline (SD)	0.568 (0.366) N = 22	0.437 (0.305) N = 27
Mean at day 90 (SD)	0.368 (0.302) N = 22	0.294 (0.158) N = 27
Mean change (SD)	–0.200 (0.274) N = 22	–0.143 (0.197) N = 27

Source: Clinical study report for the CHOC study.[7]

NOTE: N refers to number of eyes.

CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; LogMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

Complications of Corneal Cystine Crystal Deposits

Corneal Erosions

The CH 0.55% group had a higher mean corneal staining total score at baseline and experienced a greater decrease (improvement) than the CH 0.10% group (Table 13). Statistical analyses were not performed.

Intraocular Pressure

IOP was similar in both groups at baseline and decreased (improved) by a greater amount in the CH 0.55% group. Statistical analyses were not performed and there was missing data in both groups.

Table 13: Complications of Corneal Cystine Crystal Deposits

	CHOC	
	CH 0.55% Safety Set N = 30 eyes	**CH 0.10% Safety Set N = 32 eyes**
Corneal staining total score		
Mean at baseline (SD)	2.10 (4.41) N = 30	0.935 (2.59) N = 31
Mean at day 90 (SD)	0.567 (1.55) N = 30	0.290 (0.973) N = 31
Mean change (SD)	–1.53 (3.19) N = 30	–0.645 (2.52) N = 31
Intraocular pressure, mm Hg		
Mean at baseline (SD)	15.6 (4.15) N = 28	15.1 (2.90) N = 23
Mean at day 90 (SD)	15.0 (3.19) N = 27	13.0 (2.97) N = 24

Source: Clinical study report for the CHOC study.[7]

CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; SD = standard deviation.

NOTE: N refers to number of eyes.

NOTE: In eight eyes, intraocular pressure could not be measured, and the investigator instead assessed whether the eyes were normal for this parameter. All eight eyes were assessed as having normal intraocular pressure.

Patient Satisfaction With Treatment

The Comparison of Ophthalmic Medications for Tolerability questionnaire was administered to adult patients in the CH 0.55% group only and patients were asked at each visit how satisfied they had been with the medication they had been taking. At baseline, all patients had previously received topical cysteamine. Within a range of "totally dissatisfied" to "totally satisfied," two patients at baseline were "very satisfied" with their medication, two patients were "somewhat satisfied" with their medication, and one patient was "totally dissatisfied" with their medication. After 90 days of treatment with CH 0.55%, two patients were "very satisfied" with their medication and three patients were "somewhat satisfied" with their medication.

Harms

Only those harms identified in the review protocol (Table 3) are reported below. See Table 14 for detailed harms data.

Adverse Events

AEs were reported in 66.7% of the CH 0.55% group and 81.3% of the CH 0.10% group. AEs classified under eye disorders were reported in 33.3% of the CH 0.55% group and 68.8% of the CH 0.10% group. The most common eye disorders overall were ocular hyperemia (26.7% versus 31.3% in the CH 0.55% versus CH 0.10% groups), eye pain (6.7% versus 18.8%), and eye irritation (13.3% versus 12.5%). Blurred vision, eye pruritus, and keratitis were reported in 12.5% to 18.8% of the CH 0.10% group and 0% in the CH 0.55% group.

The most common non-ocular AEs were gastroenteritis (13.3% and 12.5% in the CH 0.55% and CH 0.10% groups, respectively) and nasopharyngitis (6.7% and 12.5%).

Serious Adverse Events

The SAE gastroenteritis was reported in one patient in each group. Fatigue as an SAE was reported in one patient in the CH 0.55% group. One patient in the CH 0.10% group had an SAE of corneal graft rejection and had initiated treatment 11 days after corneal transplant surgery.

Withdrawal Due to Adverse Events

One patient in the CH 0.55% group discontinued treatment at day 86 due to allergic conjunctivitis.

Mortality

There were no deaths.

Notable harms

Local Adverse Drug Reactions

At least one LADR lasting one hour was recorded in the patient diary for all patients in the CH 0.55% group and 68.8% of the CH 0.10% group. Higher percentages of patients in the CH 0.55% group versus the CH 0.10% group recorded LADRs of each severity: 100.0% versus 68.8% for mild, 80.0% versus 37.5% for moderate, 33.3% versus 12.5% for severe, and 13.3% versus 6.3% for unbearable. Higher percentages of patients in the CH 0.55% group than in the CH 0.10% group recorded the LADRs of stinging (80.0% versus 50.0%), redness (60.0% versus 43.8%), burning (66.7% versus 25.0%), blurred vision (60.0% versus 25.0%), and itching (40.0% versus 25.0%; (Table 14). LADRs reported under “other” in the CH 0.55% group (20.0% of patients) were mainly sticky eyes and sticky eyelashes.

While a higher percentage of patients in the CH 0.55% group recorded severe stinging (26.7%) than in the CH 0.10% group (12.5%), rates of severe burning, blurred vision, and itching were similar between the groups and were recorded in 13.3% or less of each group (Table 14). Unbearable stinging was recorded in 13.3% versus 6.3% of the CH 0.55% group versus the CH 0.10% group and unbearable burning and itching occurred in 6.3% of the CH 0.10% group (and none of the CH 0.55% group). A higher percentage reported LADRs without specifying severity in the CH 0.55% group than in the CH 0.10% group (46.7% versus 18.8%).

For LADRs lasting more than one hour, at least one LADR was reported in 33.3% of the CH 0.55% group and 50.0% of the CH 0.10% group (Table 14). While rates of redness (26.7% and 31.3%) and burning (13.3% and 12.5%) were similar between groups, the following LADRs lasting more than one hour were more common in the CH 0.10% group than in the CH 0.55% group: stinging (18.8% versus 6.7%), blurred vision (18.8% versus none), and itching (12.5% versus none).

Table 14: Harms

	CHOC	
	CH 0.55% Safety Set N = 15	**CH 0.10% Safety Set N = 16**
AEs		
Patients with > 0 AEs, N (%)	10 (66.7)	13 (81.3)
Eye disorders	5 (33.3)	11 (68.8)
Ocular hyperemia[a]	4 (26.7)	5 (31.3)
Eye pain[a]	1 (6.7)	3 (18.8)
Eye irritation	2 (13.3)	2 (12.5)
Blurred vision[a]	0	3 (18.8)
Eye pruritus	0	2 (12.5)
Keratitis	0	2 (12.5)
Conjunctival hyperemia	1 (6.7)	0
Conjunctivitis	0	1 (6.3)
Conjunctivitis allergic	1 (6.7)	0
Corneal neovascularization	0	1 (6.3)[b]
Dry eye	0	1 (6.3)
Lacrimation increased	1 (6.7)	0
Visual impairment	1 (6.7)	0
Other common AEs[c]		
Gastroenteritis	2 (13.3)	2 (12.5)
Nasopharyngitis	1 (6.7)	2 (12.5)
SAEs		
Patients with > 0 SAEs, N (%)	2 (13.3)	2 (12.5)
SAEs		
Gastroenteritis	1 (6.7)	1 (6.3)
Fatigue	1 (6.7)	0
Corneal graft rejection	0	1 (6.3)
WDAEs		
WDAEs, N (%)	1 (6.7)	0
Deaths		
Number of deaths, N (%)	0	0
LADRs		
Patients with > 0 LADRs lasting < 1 hour, N (%)	15 (100.0)	11 (68.8)
Stinging	12 (80.0)	8 (50.0)
Redness	9 (60.0)	7 (43.8)
Burning	10 (66.7)	4 (25.0)
Blurred vision	9 (60.0)	4 (25.0)
Itching	6 (40.0)	4 (25.0)
Other	3 (20.0)	3 (18.8)
Patients with > 0 severe LADRs lasting < 1 hour, N (%)	5 (33.3)	2 (12.5)
Stinging	4 (26.7)	2 (12.5)
Burning	2 (13.3)	2 (12.5)
Blurred vision	2 (13.3)	2 (12.5)
Itching	0	1 (6.3)
Other	1 (6.7)	0

	CHOC	
Patients with > 0 unbearable LADRs lasting < 1 hour, N (%)	2 (13.3)	1 (6.3)
Stinging	2 (13.3)	1 (6.3)
Burning	0	1 (6.3)
Itching	0	1 (6.3)
Patients with > 0 LADRs of unreported severity lasting < 1 hour, N (%)	7 (46.7)	3 (18.8)
Stinging	5 (33.3)	1 (6.3)
Redness	2 (13.3)	1 (6.3)
Burning	0	1 (6.3)
Blurred vision	2 (13.3)	2 (12.5)
Itching	0	1 (6.3)
Other	2 (13.3)	0
Patients with > 0 LADRs lasting > 1 hour, N (%)	5 (33.3)	8 (50.0)
Redness	4 (26.7)	5 (31.3)
Stinging	1 (6.7)	3 (18.8)
Burning	2 (13.3)	2 (12.5)
Blurred vision	0	3 (18.8)
Itching	0	2 (12.5)
Lacrimation increased	1 (6.7)	0
Near vision disturbance	1 (6.7)	0

Source: Clinical Study Report for the CHOC study.[7]

AE = adverse event; CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; LADR = local adverse drug reaction; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

NOTE: N refers to number of patients.

NOTE: Severe and unbearable LADRs corresponded to scores of 3 and 4, respectively (mild and moderate corresponding to 1 and 2, respectively).

NOTE: Other LADRs include sticky eyes and sticky eyelashes.

[a] Notable harm identified in the systematic review protocol.

[b] Patient had corneal neovascularization at the baseline visit.

[c] Frequency > 10% in any treatment group.

Discussion

Summary of Available Evidence

One OL, parallel group, phase III RCT met the criteria for inclusion in the CDR systematic review. In the manufacturer-sponsored CHOC study (N = 32),[7,12] patients with cystinosis that were age two years and older were randomized (1:1) to treatment with CH 0.55% or CH 0.10% ophthalmic solution for 90 days. The OCT-1 study (N = 8),[15,16] a manufacturer-sponsored, single-arm, adaptive dosage trial of CH 0.55% not meeting the systematic review criteria, is summarized in Appendix 7.

Interpretation of Results

Efficacy

Cystadrops is indicated for the treatment of CCCDs and is expected to provide clinical benefit in the improvement in cystinosis-related ocular symptoms through a reduction in these deposits. In the CHOC study, CCCDs were assessed using the IVCM total score, CCCS, and thickness by OCT. The primary end point of the CHOC study, IVCM total score, showed a statistically significantly greater improvement with CH 0.55% versus CH 0.10%. This finding was consistent in the pediatric and adult subgroups, in the PP set, and within each corneal layer. The EMA assessment report for Cystadrops[13] also found that sensitivity analyses using last observation carried forward for missing data imputation were consistent with the primary analysis. A re-analysis of IVCM total score, weighing each layer score by the thickness of the layer, was requested by the EMA and was also consistent with the original analysis.[13] This re-analysis, in addition to the consistency in score decrease across layers, helps overcome the limitation concerning the validity of applying equal weights to the individual layer scores for IVCM total score. However, there was a potential risk of bias in IVCM total score due to the lack of blinding of the investigators acquiring and selecting the images for rating which contributed some uncertainty to the magnitude of the treatment effect. There was also limited evidence, in the form of moderate and weak correlations with unvalidated patient- and investigator-rated photophobia scales, found for an association of IVCM total score with symptoms. The reliability and MCID of IVCM total score are unknown.

Corneal crystal density was also measured using CCCS, which demonstrated a statistically significantly greater improvement with CH 0.55% versus CH 0.10%. However, conclusions outside of the primary end point are limited by the lack of control for multiplicity and the potential for inflated type I error. As with IVCM total score, the reliability and MCID of CCCS are unknown and there is only limited evidence that it corresponds with photophobia. CCCS is likely less sensitive to change in corneal crystal burden than IVCM total score due to a possible ceiling effect and potentially worse reliability. Corneal crystal layer thickness was measured using OCT and showed a statistically significantly greater improvement with CH 0.55% compared with CH 0.10%. As with CCCS, evidence for this measure's association with symptoms is limited and its reliability and MCID are unknown.

The measures of corneal crystal density burden in the CHOC study were consistent with each other and supported a superior reduction over 90 days in corneal cystine crystal burden with CH 0.55% over CH 0.10%. However, the limited evidence for associations between measures of corneal cystine crystal burden and patient-important outcomes and the lack of MCIDs for these measures means that these differences are of uncertain clinical benefit. The clinical experts consulted for this review considered patient-rated photophobia

to be the most important outcome for patients in the CHOC study. The results for patient-rated photophobia showed that patients on CH 0.55% had a numerically greater improvement in photophobia compared with patients on CH 0.10% (ANCOVA model did not converge). The results for investigator-rated photophobia also showed a greater improvement with CH 0.55% versus CH 0.10%. As mentioned above, there was no control for multiplicity and potential for type I error outside of the primary end point. There was uncertainty in the effect estimates, since the scales were subjective and therefore at risk of bias in this OL trial. The validity, reliability, and MCID of the scales are unknown and the clinical experts consulted for this review were not confident that a change of a single unit on either scale would be clinically meaningful. Of note, the between-group differences on the photophobia scales observed were less than one unit. The clinical experts also considered it unusual that eight and four eyes in the CH 0.10% group worsened by one or two points on the patient- and investigator-rated photophobia scales, respectively, when noticeable progression in these patients without treatment would not be expected within 90 days. There were concerns with the validity of the scales given the lack of knowledge of how they relate to patients' ability to function or quality of life, the lack of details on how the patient-rated scale was assessed in young children, and the use of non-standardized light sources in the investigator-rated scale. Given the noted limitations, it was not possible to conclude that there was a clinically meaningful benefit in the reduction of photophobia with CH 0.55%.

Visual function is an important clinical outcome, since a decline in visual function would be expected to negatively impact patients' quality of life. While both groups experienced a numerical improvement in visual acuity and contrast sensitivity, both of these outcomes had substantial amounts of missing data. Considering the differences in visual acuity at baseline, the clinical experts consulted for this review did not consider the difference in improvement in acuity between the groups to be notable. According to the clinical experts, visual contrast sensitivity is not routinely assessed in clinical practice and its impact on patients' quality of life is not well characterized.

Corneal staining and IOP are of interest with respect to corneal erosions and angle closure glaucoma, respectively, and these are known complications of CCCDs. Improvement in corneal staining was numerically greater in the CH 0.55% group, but the between-group difference was small compared with the total range of the scale and the SDs and the clinical experts were not aware of any evidence for the validity of the scale. There were no notable differences in IOP as differences were well within the expected daily fluctuations.

There were no outcomes assessing health-related quality of life, need for corneal graft, or caregiver burden. Comparative evidence for patient satisfaction was not available.

The control arm treatment in the CHOC study was of a concentration of CH and dosage regimen expected by the clinical experts to be less effective than the treatment regimen typically used in Canada. Its comparison with Cystadrops does not inform the efficacy of Cystadrops compared with Canadian topical CH treatment or best supportive care without topical CH treatment.

Given that patients with cystinosis are expected to require treatment for corneal cystine crystal buildup throughout their lives, a 90-day treatment period does not provide sufficient evidence for the long-term efficacy and safety of Cystadrops. Continuous adherence to the treatment regimen may be a challenge for patients and their caregivers and poor adherence to treatment could be detrimental to treatment effectiveness.

In the single-arm OCT-1 study, eight patients received CH 0.55% (Cystadrops) treatment for 60 months. Patients initiated CH 0.55% treatment with a regimen of three to five instillations per day, according to their usual dosage regimen with previous CH 0.10% treatment. The number of instillations per day was increased or decreased at each study visit according to whether patients improved, worsened, or stayed the same as assessed by the investigators. The efficacy results suggested that photophobia and corneal cystine crystal burden improved and that this improvement was maintained on average over treatment duration of five years. However, the lack of a control group meant that conclusions could not be drawn regarding long-term efficacy of Cystadrops. There was a wide range in treatment adherence reported in the first 24 months of treatment as well as heterogeneity in each patient's long-term response to treatment as assessed by measures of corneal crystal burden and photophobia.

Harms

Eye disorder AEs were more common with CH 0.10% than with CH 0.55%, with the most common eye disorders being ocular hyperemia, eye pain, and eye irritation. According to the clinical experts consulted for this review, the eye disorder AEs were potentially associated with either the disease or the study medication. Non-ocular AEs occurred in one patient or none per group, with the exception of gastroenteritis and nasopharyngitis. The only ocular SAE was corneal graft rejection in a patient who initiated study treatment shortly after corneal transplant surgery. There was one withdrawal due to an AE in the CH 0.55% group due to allergic conjunctivitis which occurred near the end of the treatment period. The clinical experts did not identify any AEs, SAEs, or between-group differences in AEs that were of notable concern.

LADRs (stinging, redness, burning, blurred vision, and itching) lasting less than one hour were reported in all patients receiving CH 0.55% and most patients receiving CH 0.10% and were more common in the CH 0.55% group across all categories of severity and all types. The most common LADR lasting less than an hour categorized as severe or unbearable was stinging. Of the LADRs lasting over an hour, redness was the most common. Percentages of patients with redness and burning were similar between groups, while stinging, blurred vision, and itching were more common with CH 0.10% than with CH 0.55%. It is possible that treatment exposure of over 120% of planned instillations in four patients in the CH 0.10% group (and none in the CH 0.55% group) contributed to the difference in LADRs lasting more than one hour, though it is not possible to determine if this was the case. The clinical experts consulted for the review did not find the occurrence of any of the LADRs to be a safety concern.

Since Cystadrops could be used continuously over a patient's lifetime, the safety of long-term use of Cystadrops is important to assess. In the OCT-1 study of eight patients over five years of treatment with CH 0.55%, there was one SAE of concern (corneal neovascularization, which could have been related to disease progression or the study medication). Though the results were not conclusive, reporting of LADRs over the first 24 months of CH 0.55% treatment suggested that LADRs decreased in frequency and/or were perceived by patients to improve with longer durations of treatment.

The EMA assessment report for Cystadrops[13] stated that at the time of the assessment (March 15, 2015), 106 patients taking Cystadrops were included in the French named patient use program and had structured follow-up. Of these patients, 57 had received Cystadrops for at least six months and 28 for at least 12 months. The AEs reported were: eye irritation (8.5% of patients), eye pain (3.8%), blurred vision (3.8%), ocular hyperemia

(0.9%), lacrimation increased (0.9%), product deposit (1.9%), and instillation site discomfort (2.8%). Four patients temporarily discontinued treatment due to an AE. There were also approximately 230 patients in a separate named patient use program in countries in four continents. There were four safety reports for eye irritation, vitreous floater, corneal deposits (patient receiving Cystadrops twice daily), and eye irritation and hordeolum. None of the reported AEs in the programs were serious and no new safety signals were identified through these programs. Further details on these programs were not available.

Place in Therapy

The following is from a summary of input provided by a panel of three clinical experts, two ophthalmologists, and one nephrologist, all of whom have experience in treating patients with cystinosis. The full summary of input from the clinical panel is provided in Appendix 2.

Pharmacy-compounded ophthalmic cysteamine solutions are limited by their lack of standardization in active ingredient concentrations and methods of preparation across pharmacies, short shelf life, and regional variations in availability of pharmacies that provide these solutions. The compounded solutions need to be refrigerated at all times when not in use, and patients may unknowingly use eye drops with compromised effectiveness due to inadequate refrigeration. These solutions must be administered very frequently for maximal effectiveness (ideally, every one to two hours during waking hours). Long-term adherence to ophthalmic therapies for other conditions with once a day dosing already tends to be poor and adherence to multiple doses a day is expected to be even worse. As part of the challenges associated with adherence to this dosing regimen, children incapable of self-administration may not be able to adhere to the dosing schedule during school hours. The unmet need currently is having a commercially available, standardized, easy to access topical medication that is dosed less frequently than the compounded drops.

As with current treatment, patients with cystinosis who have ocular symptoms or complications arising from corneal cystine crystal deposition are appropriate candidates for treatment with Cystadrops. All of these patients could potentially benefit from Cystadrops treatment. Almost all patients with cystinosis will develop corneal cystine crystals and, at some point in their lives, photophobia. Cystadrops is unlikely to be used off-label.

Conclusions

Compared with CH 0.10% four times daily, CH 0.55% four times daily results in a reduction in CCCDs over a three-month period in patients with cystinosis. However, the clinical significance of these findings remains unknown due to the lack of established MCIDs for the measures of corneal cystine crystal burden and limited evidence for their association with symptoms. While the results for investigator-rated photophobia, a secondary outcome, suggested a benefit with CH 0.55% over CH 0.10%, there was no control for multiplicity of outcomes and the validity and MCID of the scale are unknown. Conclusions could not be drawn based on long-term efficacy data from a single-arm, 60-month trial due to the lack of a comparator arm.

Safety data from the RCT and the single-arm trial did not demonstrate any notable AEs, SAEs, or between-group differences in AEs, other than one SAE (corneal neovascularization) that could have been related to disease progression or CH 0.55%. Safety data suggested that LADRs upon instillation lasting less than one hour were more common with CH 0.55% than with CH 0.10%; however, long-term data for CH 0.55% suggest that LADRs may decrease in frequency and/or be perceived by patients to improve with longer durations of treatment.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff; however, no patient group input was received for this submission. The information below has been obtained from the patient group input submission for the 2018 CADTH CDR Procysbi review.[8] Procysbi is a systemic therapy indicated for the treatment of nephropathic cystinosis and the reimbursement request was for this indication.

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. They aim to advocate for health policy and a health care system that works for patients with rare disorders and their caregivers. CORD did not provide any patient input specifically for this submission; therefore, the information in this summary is based on that received for the Procysbi review.[8] At the time of that review (2017) CORD had received funding from Horizon in the two years previous to 2017; however, CORD did not declare any conflicts of interest with regard to its patient group submission.

2. Condition-Related Information

Information for the Procysbi patient input submission[8] 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 information therein was subsequently used to develop the survey. The survey was distributed by physicians, one patient fundraising group, snowballing technique, and a posting to the Cystinosis Research Foundation (USA) Facebook. In addition, the survey was posted on Survey Monkey from June 30th to July 27th, 2017 in English; however, 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 comprise this submission. The average age of patients with cystinosis was 15.1 years (range of <1 to 50 years of age), with all individual participants living in Canada and, among survey respondents, 62% were from Canada, 28% were from the US, and 5% where from elsewhere.

Patients with cystinosis most often experience a range of symptoms associated with the disease, including various gastrointestinal (GI) effects (vomiting, diarrhea, abdominal pain), muscle wasting, swallowing difficulties and gagging, halitosis, foul body odour, crystal buildup in the cornea/photosensitivity (reported as occurring “much or severe” in 44% of survey respondents and as “some” in 50% of survey respondents), extreme thirst and urination, reduced cognitive abilities, and rickets/softening of bones. Secondary impacts of the disease include kidney failure (which can occur in adolescence and 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 (a systemic therapy similar to Procysbi and with the same active ingredient, but with an immediate-release formulation which requires the patients/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 the family members (not just the caregivers and the patients). In addition to this, patients and their families can experience reduced concentration and isolation (both socially and emotionally) due to the 24 hours per day/seven days of the week of vigilance required for care plus the regular clinic visits, trips to the physiotherapist (to deal with weakened muscles and back pain), speech therapist, 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 due to the direct cost of medications, supplements and other supplies, non-reimbursed costs of health care visits, household expenses for modifications or other repairs, and the loss of income when a parent has to reduce their work hours or quit their job to provide continuous homecare. 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.” In addition, the following quotation highlights some of the concerns regarding the complications (including crystal buildup in the cornea), “Though we rarely deal with acute emergency situations now that he is on a well monitored regime of medication (e.g.,Cystagon) and supplements, the multitude of complications associated with his progressive disease are a constant worry - from a high risk of broken bones, to crystal build up in the cornea, to kidney failure and reduced cognitive ability, and even sterility and the list goes on..”

As the aforementioned indicates, 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 (e.g., Cystagon) 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 at school and socially). In those caregivers that have a spouse with cystinosis, there is often an increased burden in having to take on the bulk of financial and family responsibilities. All of this leads to further isolation of the caregiver, family and financial stress issues, and an increased burden by having to take time off work.

3. Current Therapy-Related Information

Among the 32 patients that 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. Patients understand that Cystagon saves the lives of patients; however, it does not resolve all of the clinical problems (including deficits in sight, hearing, and cognition) and it is challenging to strictly adhere to the treatment regimen.

Additional medications and supplements are also part of the treatment paradigm, with many patients taking nutrient replacements (sodium, potassium citrate, phosphate, and vitamin D), medications to aid with stomach aches and heartburn, and anti-vomiting medications. Some patients also have taken growth hormone therapy and hormone supplements. In terms of other treatments, some patients noted that they were on dialysis and more than half of patient respondents claimed they had or were indicated for a kidney transplant. There was no information provided in the Procysbi patient input submission regarding experience with the treatment of corneal cystine deposits.

4. Expectations About the Drug Being Reviewed

There was no patient input for this submission; therefore, there was no information available regarding expectations for Cystadrops.

Appendix 2: Clinical Panel Input Summary

A panel was convened by CADTH of three clinical experts, two ophthalmologists, and one nephrologist, all of whom have experience in treating patients with cystinosis. The following summary of the input provided by the panel was prepared by CADTH.

Current Standard of Care

Patients with nephropathic cystinosis generally receive confirmation of diagnosis by demonstrating high levels of leukocyte cystine (expressed as nmol of half-cystine per mg protein) following classic presentation of the disease, which includes findings consistent with renal Fanconi syndrome. The presence of corneal cystine crystals can provide further evidence to confirm the diagnosis. In patients with nephropathic cystinosis, genetic testing is becoming more standard in Canada. Genetic testing is particularly advantageous for infant siblings of affected patients as it can provide a rapid diagnosis in the first few days of life (when white blood cell cystine levels are not interpretable), thereby allowing for early treatment initiation. However, genetic confirmation is not required to diagnose cystinosis and may not be readily available in all provinces.

Corneal cystine crystals and resultant symptoms develop almost universally in patients with cystinosis, regardless of cystinosis type. In Canada, there are no commercial products available for the treatment of corneal cystine crystal deposits and pharmacy-compounded solutions represent the only treatment option. These solutions typically contain 0.55% cysteamine hydrochloride and are administered every one to two hours during the day. Treatment with cysteamine eye drops continues throughout the patient's lifetime. Currently the impetus for treatment with topical cysteamine is the presence of ocular symptoms, especially glare and photophobia, rather than the detection of corneal crystals alone. The presence of other corneal complications such as filamentary keratitis and recurrent erosions would also spur a recommendation for treatment. There are no formal treatment guidelines for the ocular manifestations of cystinosis.

Canadian patients with cystinosis and ocular problems see an ophthalmologist every six to 12 months, depending on the presence of symptoms, and receive a full ocular examination. The ocular exam typically includes a dilated fundus exam, a slit-lamp exam for corneal crystals, and assessments of IOP and vision. Imaging with OCT may be performed if there are concerns about retinal problems.

Unmet Needs With Current Therapies

Compounded ophthalmic cysteamine solutions are limited by their lack of standardization in active ingredient concentrations and methods of preparation across pharmacies, short shelf life, and regional variations in availability of pharmacies that provide these solutions. The compounded solutions need to be refrigerated at all times when not in use, and patients may unknowingly use eye drops with compromised effectiveness due to inadequate refrigeration. These solutions must be administered very frequently for maximal effectiveness (ideally, every one to two hours during the waking). Long-term adherence to ophthalmic therapies for other conditions with once a day dosing already tends to be poor and adherence to multiple doses a day is expected to be even worse. As part of the challenges associated with adherence to this dosing regimen, children incapable of self-administration may not be able to adhere to the dosing schedule during school hours. The

unmet need currently is having a commercially available, standardized, easy to access topical medication that is dosed less frequently than the compounded drops.

Place in Therapy for Cystadrops

As with current treatment, patients with cystinosis who have ocular symptoms or complications arising from corneal cystine crystal deposition are appropriate candidates for treatment with Cystadrops. All of these patients could potentially benefit from Cystadrops treatment. Almost all patients with cystinosis will develop corneal cystine crystals and, at some point in their lives, photophobia. Cystadrops is unlikely to be used off-label.

Considerations for Appropriate Use of Cystadrops in Clinical Practice

Treatment Initiation

Diagnosis of cystinosis and corneal cystine crystal deposits

The panel considered that patients should have a diagnosis of cystinosis through the test for white blood cell cystine or through genetic testing. Patients must demonstrate corneal cystine crystal deposits, which are readily detected on a slit-lamp examination.

Symptoms and complications of corneal cystine crystal deposits

Further, the panel considered that patients should have symptoms or complications associated with corneal cystine crystal deposits as a requirement for treatment with Cystadrops. The chief symptoms associated with the accumulation of corneal cystine crystals are photophobia and glare. To ensure that the patient's symptoms are those that can be treated with Cystadrops, other possible causes of these symptoms should be ruled out during clinical examination. Starting Cystadrops treatment when patients are still asymptomatic may provide benefit by preventing or delaying the inevitable constellation of symptoms and morbidity associated with corneal crystal deposition. However, the clinical panel noted that symptomatic patients should have priority for treatment.

No clinical factors were identified that would preclude any patient with cystinosis from being considered as a candidate for Cystadrops treatment. Patient adherence to treatment and the amount of corneal cystine crystal accumulation are potential factors that may influence the benefit received from Cystadrops treatment; however, there is insufficient evidence to support a recommendation based on these factors. Also, the rarity of the disease makes it difficult to identify subpopulations of patients more likely to benefit from, or in greater need of, Cystadrops.

It is possible, though not proven, that patients with poor adherence to compounded cysteamine eye drops due to the burdensome dosage regimen are in greater need of Cystadrops and would receive greater benefit from Cystadrops should their adherence to ophthalmic treatment improve. The panel considered that patients most at risk of low adherence to compounded cysteamine eye drops are children attending school who are incapable of self-administering eye drops and adolescent patients. In the former group, a dosage regimen of four times a day may be more feasible than one that is every one to two hours during the day. The lack of need for refrigeration of Cystadrops may minimize a potential barrier to adherence or prevent the use of ineffective eye drops.

Given the mode of administration, one could speculate that older patients with corneal crystal deposits that have been established for decades would receive less benefit from

Cystadrops than young patients with newly developed corneal crystals, as the active ingredient may not reach the deeper layers of the cornea in concentrations that are efficacious. One study following 10 patients ranging in age from one to 32 years over eight to 41 months of treatment with topical cysteamine eye drops demonstrated improvements in corneal crystals under slit-lamp photography in all patients.[14] Therefore, there is some evidence that older patients with substantial corneal crystal burdens can benefit from treatment with eye drops containing the same active ingredient as Cystadrops.

Prescribing physician

The panel considered ophthalmology to be the appropriate specialty to prescribe and monitor the use of Cystadrops. Any ophthalmologist who is treating patients with cystinosis for ocular problems will have the necessary expertise to prescribe Cystadrops and perform the eligibility assessments.

Ongoing Treatment

Assessment of initial treatment response

Given the 90-day duration of the CHOC study, an initial assessment for treatment response after three months was found to be appropriate by the panel. The panel considered an improvement in symptoms associated with corneal cystine crystals, an improvement on ocular examination, or both as sufficient evidence indicating a positive treatment response that would justify continued treatment with Cystadrops. An improvement in photophobia or other symptoms does not need to be demonstrated on a specific scale: a subjective improvement would suffice. An improvement on ocular examination could be demonstrated by a reduction in corneal crystals visualized with a slit-lamp or IVCM, or corneal crystal depth measured with OCT. For slit-lamp examination or IVCM, the use of a specific scale or scoring system would not be necessary. Practically speaking, OCT and slit lamp are the easiest and most accessible means for assessing corneal cystine crystals. Slit lamp is routinely used and OCT is available for most clinicians treating corneal cystine crystals. In contrast, IVCM cannot be performed in young children, is not available at all centres, and is not used in routine clinical practice.

The panel agreed that treatment should not be continued in a patient who does not experience an improvement on any of these measures. The panel also noted that patients may have little motivation to continue treatment if they do not experience an improvement. The panel recommended against any further specifications for assessing treatment response due to unknowns associated with the rarity of the condition and potential differences across centres where patients are treated.

Ongoing patient assessments

The panel considered ongoing assessments every 12 months as reasonable for reimbursement purposes following the initial treatment response assessment. It was noted that patients with cystinosis typically visit an ophthalmologist at least as often as once every 12 months. With continued treatment, patients will eventually plateau or reach a steady state in terms of improvement and cystine crystals may never be completely eliminated from their corneas. As long as the physician determines that some clinical benefit is being maintained, the patient should continue to receive Cystadrops treatment. As with the initial treatment response, this clinical benefit can be demonstrated through symptoms or ocular examination.

Treatment discontinuation

The panel determined that clinical worsening while on treatment, in terms of symptoms or ocular examination, would be sufficient reason to discontinue Cystadrops treatment after ensuring that the patient is preparing and using the medication appropriately. It is important to note that it is common for patients to stop using cysteamine eye drops or to not adhere to the full dosage regimen for prolonged periods of time. Physicians often need to encourage their patients to adhere to the dosage regimen. There is a risk of clinical worsening with poor adherence, but patients would still be expected to receive clinical benefit from treatment at a later point should they resume the full dosage regimen.

In a patient who experiences an adverse reaction to the medication, the physician may temporarily discontinue treatment until the problem resolves or other problems are addressed. Such a patient could eventually resume treatment unless it was clear that they are not able to tolerate the medication due to sensitivity to a component of the medication (e.g., the preservative).

Appendix 3: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) PubMed **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 15, 2019
Alerts:	Biweekly search updates until project completion
Study Types:	No publication type filters were applied
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic;
or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings	
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.nm	Name of substance word
.rn	Registry number
.dq	Candidate term word
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily

MULTI-DATABASE STRATEGY

Line #	Search Strategy
1	Cysteamine/
2	(cystadrop* or cysteamin* or cysteaminehydrochlorid* or Cysteaminhydrochlorid* or cysteamineHCL or cysteaminechlorohydrate* or cysreinamine* or decarboxycysteine* or cysteaminium chloride* or 2aminoethanethiol or 2 aminothioethanol or Cysteinamine* or mercaptamin* or mercaptaminehydrochloride* or mercamine* or mercaptoethylamine* or mercaptoamine* or MEA or becaptan* or bekaptan* or lambraten* or riacon* or "EINECS 200 463 0" or EINECS 2004630 or EINECS2004630 or EINECS 205 858 1 or EINECS 2058581 or EINECS2058581 or HSDB 7353 or HSDB7353 or L 1573 or L1573 or A 889 or A889 or AI3 26089 or AI326089 or EC 205 858 1 or EC 2058581 or EC2058581 or WR 347 or WR347 or CI 9148 or CI9148 or NSC 647528 or NSC647528 or 5UX2SD1KE2 or IF1B771SVB).ti,ab,kf,ot,rn,nm.
3	or/1-2

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
4	Cystinosis/
5	(cystinosis or cystinoses or ((cystine or cystinosin* or abderhalden* or lignac fanconi*) adj4 (diathesis or diatheses or disease* or nephropathic* or defect* or syndrome*))).ti,ab,kf,ot.
6	or/4-5
7	3 and 6
8	7 use medall
9	*mercaptamine/
10	(cystadrop* or cysteamin* or cysteaminehydrochlorid* or Cysteaminhydrochlorid* or cysteamineHCL or cysteaminechlorohydrate* or cysreinamine* or decarboxycysteine* or cysteaminium chloride* or 2aminoethanethiol or 2 aminothioethanol or Cysteinamine* or mercaptamin* or mercaptaminehydrochloride* or mercamine* or mercaptoethylamine* or mercaptoamine* or MEA or becaptan* or bekaptan* or lambraten* or riacon* or "EINECS 200 463 0" or EINECS 2004630 or EINECS2004630 or EINECS 205 858 1 or EINECS 2058581 or EINECS2058581 or HSDB 7353 or HSDB7353 or L 1573 or L1573 or A 889 or A889 or AI3 26089 or AI326089 or EC 205 858 1 or EC 2058581 or EC2058581 or WR 347 or WR347 or CI 9148 or CI9148 or NSC 647528 or NSC647528 or 5UX2SD1KE2 or IF1B771SVB).ti,ab,kw,dq.
11	or/9-10
12	cystinosis/
13	(cystinosis or cystinoses or ((cystine or cystinosin* or abderhalden* or lignac fanconi*) adj4 (diathesis or diatheses or disease* or nephropathic* or defect* or syndrome*))).ti,ab,kw,dq.
14	or/12-13
15	11 and 14
16	15 use oemezd
17	16 not conference abstract.pt.
18	8 or 17
19	remove duplicates from 18

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. [Search -- Studies with results | Cystadrops Search -- Studies with results | cysteamine OR mercaptamine AND cystinosis
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms – Cystadrops, cysteamine, and mercaptamine

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	January 03, 2019 – January 10, 2019
Keywords:	Cystadrops, cysteamine, cysteamine hydrochloride, mercaptamine, mercaptamine hydrochloride
Limits:	Publication years: all

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey Matters: A Practical Tool for Evidence-based Searching* (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
- Clinical Trial Registries
- Databases (free)
- Internet Search
- Background.

Appendix 4: Excluded Studies

Table 15: Excluded Studies

Reference	Reason for Exclusion
Labbé A, Baudouin C, Deschenes G, et al. A new gel formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis: the Cystadrops OCT-1 study. Mol Genet Metab. 2014	Irrelevant study design. Included as a supplemental issue.
Tsilou ET, Thompson D, Lindblad AS, et al. A multi-centre randomised double masked clinical trial of a new formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis. Br J Ophthalmol. 2003 Jan;87(1):28-31.	Irrelevant intervention.

Appendix 5: Detailed Outcome Data

Table 16: Efficacy Outcomes in the Pediatric Subgroup

	CHOC	
	CH 0.55% FAS N = 16	**CH 0.10% FAS N = 22**
Corneal Cystine Crystal Score		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
P value	[redacted]	
Crystal layer thickness by OCT, µm		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
P value	[redacted]	
Patient-assessed photophobia		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
P value	[redacted]	
Investigator-assessed photophobia		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
P value	[redacted]	

Source: Clinical study report for the CHOC study.[7]

CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; FAS = full analysis set; NR = not reported; OCT = optical coherence tomography; SD = standard deviation.

NOTE: Each pair of eyes was considered as repeated measurements within each patient.

NOTE: An analysis of covariance model was used which included treatment group as a factor and baseline value as a covariate.

[a] *P* value is provided for descriptive purposes only.

[b] Model did not converge.

Table 17: Efficacy Outcomes in the Adult Subgroup

	CHOC	
	CH 0.55% FAS N = 14 eyes	**CH 0.10% FAS N = 10 eyes**
Corneal Cystine Crystal Score	N = 14 eyes	N = 9 eyes
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
P value	[redacted]	
Crystal layer thickness by OCT, µm	N = 14 eyes	N = 10 eyes
Mean at baseline (SD)	[redacted]	[redacted] N = 9 eyes
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted] N = 9 eyes

	CHOC	
P value	[redacted]	
Patient-assessed photophobia	N = 14 eyes	N = 9 eyes
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
P value	[redacted]	
Investigator-assessed photophobia	N = 14 eyes	N = 9 eyes
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
P value	[redacted]	

Source: Clinical study report for the CHOC study.[7]

CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; FAS = full analysis set; NR = not reported; OCT = optical coherence tomography; SD = standard deviation.

NOTE: Each pair of eyes was considered as repeated measurements within each patient.

NOTE: An analysis of covariance model was used which included treatment group as a factor and baseline value as a covariate.

[a] *P* value is provided for descriptive purposes only.

[b] Model did not converge.

Table 18: In Vivo Confocal Microscopy Score by Corneal Layer

	CHOC	
	CH 0.55% IVCM FAS N = 22 eyes	**CH 0.10% IVCM FAS N = 20 eyes**
IVCM score, epithelium		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	–0.949 (1.15) N = 20	–0.202 (0.848) N = 17
IVCM score, basal epithelium		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	–0.464 (0.595) N = 20	–0.196 (0.666) N = 17
IVCM score, Bowman's layer		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	–0.527 (0.678) N = 20	–0.058 (0.762) N = 17
IVCM score, superficial stroma		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	–0.816 (0.730) N = 20	–0.053 (0.918) N = 17

	CHOC	
IVCM score, medium stroma		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	–1.02 (0.756) N = 20	0.071 (1.16) N = 17
IVCM score, deep stroma		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	–0.730 (0.902) N = 20	–0.016 (0.851) N = 17
IVCM score, endothelium		
Mean at baseline (SD)	[redacted]	[redacted]
Mean at day 90 (SD)	[redacted]	[redacted]
Mean change (SD)	–0.100 (0.447) N = 20	0.0 (0.000) N = 17

Source: Clinical study report for the CHOC study.[7]

CH = cysteamine hydrochloride; CHOC = Cysteamine Hydrochloride for nephropathic Cystinosis study; FAS = full analysis set; IVCM = in vivo confocal microscopy; SD = standard deviation.

NOTE: N refers to number of eyes.

NOTE: IVCM data were missing for one patient at baseline in the CH 0.55% group in addition to one patient and one eye in second patient at day 90 in the CH 0.10% group.

Appendix 6: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Corneal crystal density by in vivo confocal microscopy (IVCM)
- Cystinosis corneal crystal score (CCCS) by slit-lamp
- Corneal crystal layer thickness by anterior segment optical coherence tomography (AS-OCT)
- Photophobia scales (patient-rated and clinician-rated)

Findings

Table 19: Validity of Outcomes

Instrument	Type	Evidence of Validity	MCID	References
Corneal cysteine crystal density by IVCM total score	IVCM is a non-invasive, microscopic technique used to assess cellular-level changes in the cornea. This has been used to also assess crystal deposition and distribution. The IVCM total score (composite score obtained by summing up the individual layer scores) ranges between 0 and 28, with higher scores indicating higher crystal densities/accumulations.	No	Unknown	Labbé et al., 2009[18] Liang et al., 2015[17]
CCCS by slit-lamp	The CCCS is a score between 0 (clear view) and 3.00 (tightly packed crystals), at increments of 0.25. It is a semi-quantitative analysis that compares individual slit-lamp photographs with a library of previously graded slit-lamp photographs of images with varying crystal densities.	No	Unknown	Gahl et al., 2000[14] Liang et al., 2015[17]
Crystal layer thickness in the central cornea by AS-OCT	AS-OCT is a non-contact method for acquiring high-resolution corneal images. Corneal crystal layer thickness in the central cornea is measured manually on the images using the OCT system's software.	No	Unknown	Labbé et al., 2009[18] Liang et al., 2015[17]
Photophobia scales (patient-rated and clinician-rated)	Both scales are ordinal grading scales ranging from 0 to 5, with higher scores indicating worse or more severe photophobia.	No	Unknown	Liang et al., 2015[17]

AS-OCT = anterior segment – optical coherence tomography; CCCS = Corneal Cystine Crystal Score; IVCM = in vivo confocal microscopy; MCID = minimal clinically important difference.

Corneal Crystal Density by In Vivo Confocal Microscopy (IVCM)

IVCM is a non-invasive technique used to assess cellular-level changes in the cornea.[18,19] Using a laser scanning confocal microscope, 4-dimensional high-resolution images of the cells and structures of the cornea are obtained at varying depths.[19] Images are taken en face, meaning that the thin-sliced images are parallel to the epithelial surfaces; hence, this allows for a continual investigation throughout the full depth of corneal tissue by varying the depth of focus.[19]

The Rostock Cornea Module of the Heidelberg Retina Tomograph was used in the CHOC and OCT-1 studies as well as in previous studies[17,18] to examine corneal cystine crystal density. In this technique, a 60x immersion lens is used to obtain 384 x 384 pixel images that cover a 400 x 400 µm area.[18] Investigators examine each eye for less than 5 minutes once they have added one drop each of a topical anesthetic and gel tear substitute into the lower conjunctival fornix.[18] Approximately 200 IVCM images are obtained in the central cornea, starting from the superficial epithelial layer through to the endothelium. These are evaluated for crystal density using reference images in each corneal layer (including the superficial and basal epithelium, Bowman's layer, the superficial, middle, and deep stromal layers, and the endothelium; for a total of seven corneal layers). These reference images have been previously assigned grades from 0 to 4[18] (0 = no crystals; 1 = less than 25% of deposits in the images; 2 = 25% to 50% of deposits in the images; 3 = 50% to 75% of deposits in the images; and 4 = 75% to 100% of deposits in the images).[7] A composite score, IVCM total score, is obtained by summing up the individual layer scores and it ranges between 0 and 28 (with higher scores indicating greater crystal density and/or burden).[7]

In order to determine if corneal tissue changes correlated with photophobia, Liang et al.[17] examined 20 patients with infantile nephropathic cystinosis (mean age 17.10 years; SD of 9.55 years; range of seven to 37 years) using IVCM, CCCS, and AS-OCT. Photophobia was both patient- and clinician-rated (see subsequent section on photophobia scales) and IVCM, CCCS, and AS-OCT assessments were performed. A weak but statistically significant correlation (R^2 = 0.27; P = 0.0006) was observed between IVCM total score and central corneal crystal layer thickness as a percentage of central corneal thickness (using AS-OCT). In addition, weak and moderate (respectively) statistically significant correlations were observed between IVCM total score and the clinician- and patient-rated photophobia scores (R^2 = 0.21; P = 0.003 and R^2 = 0.33; P = 0.0001, respectively).

While IVCM is able to resolve individual corneal cystine crystals, IVCM total score has not been shown to correlate with any validated measures of corneal crystal-related symptoms. No MCID associated with IVCM total score and no evidence for its reliability was identified in the aforementioned studies[17,18] or any other literature. Another limitation associated with IVCM is that it cannot be used in young children or very sensitive patients due to eye contact needed using this procedure.[17]

Cystinosis Corneal Cystine Crystal Score (CCCS) by Slit Lamp

In order to evaluate corneal crystals, the investigators used the method by Gahl et al.,[14] whereby, slit-lamp biomicroscopy was used in order to obtain images with which they could compare to a library of slit-lamp photographs of corneas with different crystal densities. The biomicroscope was equipped with a photo–slit-lamp with additional accessories (including beam splitters, side-arm adapters, two cameras, and stereoscopic accessories). A moderately wide slit beam of 5 mm alongside 25x magnification was used to obtain the

images.[14] The CCCS was determined by the investigator in each eye with a possible range of 0.00 (clarity at the centre) to 3.00 (greatest recognizable crystal density) in increments of 0.25.[14]

No official study was identified in the supplemental search that validated the CCCS or deemed it a reliable method. Gahl et al.[14] examined corneal densities using the CCCS and slit-lamp method in 170 patients with nephropathic and non-nephropathic cystinosis, some of whom received topical cysteamine therapy. They observed a roughly linear trend (without accompanying statistical analysis) of increasing crystal density up to the age of six that appeared to level off at the age of 12 (median CCCS of 3.00).[14] The authors noted that this plateau was probably due to their inability to ascertain different crystal density grades when the corneas were packed too tightly with crystals;[14] hence, indicating a potential limitation in this measurement approach. The investigators also observed that the appearance of photophobia corresponds roughly to late childhood, when a CCCS of about 2.50 is obtained.[14]

Weak to moderate correlations were observed by Liang et al. in the aforementioned study of 20 patients between CCCS and patient-rated photophobia (R^2 = 0.20; P = 0.0043) and clinician-rated photophobia (R^2 = 0.61; P < 0.0001).[17] No MCID associated with CCCS was identified in the aforementioned studies[14,17] or any other literature.

Corneal Crystal Layer Thickness by Anterior Segment Optical Coherence Tomography (AS-OCT)

AS-OCT is a non-contact method used for high-resolution corneal scanning and analysis. In a study by Liang et al., twenty-six thousand A-scans were performed per second with a 15 µm and a 5 µm transverse and axial resolution, respectively.[17] A corneal adapter module lens was used in front of the objective lens in order to focus the OCT beam on the anterior segment.[17] A high-resolution program was used to ascertain the images and corneal crystal layer thickness was measured on the images using the manual caliper tool in the AS-OCT software package.[17] Corneal crystal layer thickness can also be expressed as a percentage of corneal central corneal thickness as measured on a corneal pachymetry map using the same OCT system.[17,18]

Moderate correlations were observed by Liang et al. between AS-OCT-measured corneal crystal layer thickness as a percentage of corneal central corneal thickness and patient-rated photophobia (R^2 = 0.49; P < 0.0001) and clinician-rated photophobia (R^2 = 0.33; P = 0.0001).

No MCID associated with corneal crystal layer thickness by AS-OCT and no evidence for its reliability was identified in the aforementioned studies[17,18] or any other literature.

Photophobia Scales (Patient-Rated and Clinician-Rated)

Self (Patient)-Rated Photophobia Grading Scale

The patient-rated photophobia grading scale used in the CHOC study was[7,20] the six-point scale defined in Liang et al.[17] as follows:

- 0 = no photophobia, no discomfort (none)
- 1 = slight difficulty with light causing occasional eye blinking (trace)
- 2 = slight difficulty with light causing regular eye blinking (mild)
- 3 = moderate difficulty with light requiring wearing sunglasses (moderate)

- 4 = severe difficulty with light requiring wearing sunglasses in a quasi-permanent manner (severe)
- 5 = extreme difficulty with light requiring the patient to remain inside, cannot bear natural light even with sunglasses (extreme)

Liang et al.[12] aimed to determine whether there was any correlation between photophobia and corneal tissue changes (i.e., cystine crystal deposition) in 20 patients with infantile nephropathic cystinosis. Moderate correlation was observed between photophobia and age (R^2 = 0.30; P = 0.0003). As mentioned above, moderate correlations were found between patient-rated photophobia and IVCM total score (R^2 = 0.33; P = 0.0001) and between patient-rated photophobia and AS-OCT-measured corneal crystal thickness as a percentage of central corneal thickness (R^2 = 0.49; P < 0.0001).[17] A weak correlation was also found between patient-rated photophobia and CCCS (R^2 = 0.20; P = 0.0043).[17]

Clinician-Rated Photophobia Grading Scale

The clinician-rated photophobia grading scale used in the CHOC and OCT-1 studies is described, as follows:

- 0 = no photophobia (none)
- 1 = photophobia to light from indirect ophthalmoscope (trace)
- 2 = photophobia to light from slit-lamp beam (mild)
- 3 = photophobia to light from torch (moderate)
- 4 = photophobia needing dark glasses even indoors (severe)
- 5 = unable to open eyes even indoors (extreme)

No evidence of validity, reliability, or an MCID associated with the patient-rated or the clinician-rated photophobia grading scale were identified in the aforementioned study[17] or any other literature.

Appendix 7: Summary of Other Studies

Introduction

Given the potential for lifelong treatment with Cystadrops due to the unrelenting nature of cystinosis and corneal cystine crystal deposition, it is important to assess the long-term efficacy and safety of treatment with Cystadrops. The duration of the included randomized controlled trial (the CHOC study) was 90 days and therefore inadequate for assessing the effects of long-term treatment with Cystadrops. Before the CHOC study, a phase I/IIa single-arm study (Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis [OCT-1] study, N = 8, conducted at two centres in France from 2008 to 2013 by Orphan Europe SARL [part of the Recordati Group]) was conducted in which patients received Cystadrops treatment for 60 months. The objectives of the OCT-1 study were: "to establish the safety of Cystadrops over a defined period," "to find the lowest effective dose according to an empiric adaptive dose regimen algorithm," and "to evaluate the response to Cystadrops treated at a defined period."

Table 20: Details of Study

		OCT-1
Designs and Populations	**Study Design**	OL, single-arm, dose adaptive phase I/IIa study
	Locations	Two centres in France
	Number of Patients	8
	Inclusion Criteria	• Age ≥ 3 years • Diagnosis of cystinosis based on previous WBC cystine concentration > 1.5 nmol half-cystine per mg protein • Presence of corneal crystal deposits by slit-lamp exam within 3 months prior to inclusion • Ability to comply with 3 to 6 instillations daily • Agreement to attend 16 assessment visits within 60 months[a] • Topical treatment with CH 0.10% reference formulation for ≥ 1 month prior to inclusion (≥ 3 instillations a day)
	Exclusion Criteria	• Uncontrolled hepatic disorder, cardiovascular disease, neurologic disease, or cancer • Clinically significant (according to the investigator) laboratory tests out of normal range • History or presence of alcohol abuse or drug addiction • Patients likely to be non-compliant for study procedures or for whom a long-term follow-up seems difficult to achieve
Drugs	**Run-In Phase**	1 drop of CH 0.10% reference formulation in each eye 3 to 6 times a day
	Treatment Phase	1 drop of CH 0.55% viscous solution (Cystadrops) in each eye according to the dosage established during run-in. The number of instillations per day could be adapted according to a pre-specified algorithm at each visit (after 1, 3, 6, 9, and 12 months of treatment, every 6 months subsequently to month 48, and month 60).
Duration	**Phase**	
	Run-in	30 days
	Treatment	60 months
Outcomes	**Primary End Point**	Change in IVCM total score from baseline
	Other End Points	• IVCM total score • IVCM individual corneal layer scores • Photophobia graded on a 6-point scale by the investigator

		OCT-1
		• Corneal cystine crystal score by slit-lamp examination • Corneal cystine crystal layer thickness by IVCM • Corneal cystine crystal layer thickness by OCT • AEs, SAEs • Diary card for ocular symptoms (redness, blurring, irritation, itching, burning, discomfort, and pain) following each instillation • Pain at instillation on a visual analogue scale • Intraocular pressure • Visual acuity using the logMAR scale • Visual contrast sensitivity • Intraocular pressure
NOTES	**Publications**	Labbé et al., 2014[15]

Source: Clinical study report for the OCT-1 study.[16]

AE = adverse event; CH = cysteamine hydrochloride; IVCM = in vivo confocal microscopy; logMAR = logarithm of the minimum angle of resolution; nmol = nanomole; OCT = optical coherence tomography; OCT-1 = Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis; OL = open label; RCT = randomized controlled trial; SAE = serious adverse event; WBC = white blood cell.

[a] The study was extended from 90 days to 60 months through protocol amendments.

Description of Study

Patients were recruited from two sites in Paris, France and attended study assessment visits at a third site in Paris. After a 30-day run-in period with CH 0.10% ophthalmic solution treatment, patients initiated treatment with CH 0.55% viscous ophthalmic solution (Cystadrops) and continued treatment for 60 months. Efficacy and safety outcomes were assessed at study visits during the treatment period at baseline, months 1, 3, 6, 9, and 12, every six months subsequently to month 48, and month 60.

The dosage regimen for CH 0.10% during the run-in period was based on the patient's accustomed dosage regimen (three to six times daily) and patients initiated CH 0.55% treatment with the run-in period dosage regimen. At each assessment visit, the number of instillations per day (same in both eyes) was adjusted according to an algorithm based on ophthalmic assessments.

The original treatment period was 180 days and was extended four times through protocol amendments. The first amendment extended the treatment period to 12 months due to a favourable benefit/risk profile and additional rules for dosage adjustments at later visits were introduced. One of the amendments changed the study objectives and the primary objective was revised from "to compare safety of Cystadrops versus the patient's usual dose regimen reference treatment" to "to establish the safety of Cystadrops along the treatment over the defined period."

Baseline Characteristics

Details on patient characteristics at study entry are presented in Table 21. All patients were already receiving systemic treatment with cysteamine bitartrate (Cystagon) and topical treatment with CH 0.10% eye drops at the start of the study. All patients had a diagnosis of infantile onset nephropathic cystinosis and seven of the patients were children at the time of study entry. Mean disease duration prior to study entry was 10.6 years and ranged from 6.0 to 19.0 years. The median duration of previous treatment with CH 0.10% eye drops was [redacted]. Most patients ([redacted]) were taking CH

0.10% three times a day at study entry and adherence to topical treatment during run-in was [redacted].

Table 21: Summary of Patient Characteristics at Start of Study

	OCT-1 N = 8 FAS
Male, n (%)	2 (25.0)
Female, n (%)	6 (75.0)
Age, years	
Mean (SD)	12.1 (4.6)
Median (range)	11.5 (7.0 to 21.0)
Age category, n (%)	
< 12 years	4 (50.0)
12 to 17 years	3 (37.5)
≥ 18 years	1 (12.5)
Disease duration, years	
Mean (SD)	10.6 (4.2)
Median (range)	10.0 (6.0 to 19.0)
Age at diagnosis, months	
Mean (SD)	17.5 (10.8)
Median (range)	15.5 (0.0 to 38.0)
Previous renal transplantation, n (%)	3 (37.5)
Mean age at renal transplantation (SD), years	[redacted]
Duration of previous CH 0.10% topical treatment, months	
Mean (SD)	[redacted]
Median (range)	[redacted]
Number of CH 0.10% instillations per day at study inclusion, n (%)	
3	[redacted]
4	[redacted]
5	[redacted]
Duration of CH 0.10% topical treatment during run-in, days	
Mean (SD)	[redacted]
Median (range)	[redacted]
Run-in treatment adherence including days of interruption, %	
Mean (SD)	[redacted]
Median (range)	[redacted]
Run-in treatment adherence during days of treatment intake only, %	
Mean (SD)	[redacted]
Median (range)	[redacted]
Mean WBC cystine (SD), nmol ½ cystine per mg of protein	
At start of run-in	[redacted]
At start of treatment	2.6 (1.9)

Source: Clinical study report for the OCT-1 study.[16]

NOTE: N refers to number of patients.

CH = cysteamine hydrochloride; FAS = full analysis set; OCT-1 = Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis; SD = standard deviation; WBC = white blood cell.

Ocular characteristics of patients, summarized on a per eye basis at the start of the run-in and treatment periods, are provided in Table 22. Out of a possible score of 0 to 28, the mean IVCM total score was 11.38 at baseline (start of the treatment period). Out of a possible score of 0 to 3.00, most patients had a CCCS of 3.00, with the remaining patients having a CCCS of 2.75. Out of a possible score of 0 to 5, the mean photophobia score was 2.50 at baseline with a range of 1 to 4. Compared with patients in the CHOC study, patients in the OCT-1 study were younger, had worse measures of corneal cystine crystal burden, and worse investigator-rated photophobia at baseline. The ocular characteristics were similar between the two time points.

Table 22: Summary of Ocular Characteristics at Start of Study and Start of Treatment

	OCT-1 N = 16 eyes FAS	
	Start of run-in phase	**Start of treatment**
IVCM total score		
Mean (SD)	11.38 (3.30)	11.38 (2.94)
Median (range)	12.00 (6 to 16)	11.00 (7 to 18)
Corneal cystine crystal score		
Mean (SD)	2.94 (0.11)	2.91 (0.13)
Median (range)	3.00 (2.75 to 3.00)	3.00 (2.75 to 3.00)
Corneal cystine crystal layer thickness by IVCM, µm		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Corneal cystine crystal layer thickness by OCT, µm		
Mean (SD)	301.4 (105.1)	306.4 (98.9)
Median (range)	268.0 (202 to 545)	266.0 (200 to 531)
Photophobia score by investigator, 0 to 5		
Mean (SD)	2.75 (1.13)	2.50 (0.89)
Median (range)	2.50 (1 to 4)	2.50 (1 to 4)
Pain at instillation, 0 to 100 mm VAS		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Visual acuity, logMAR scale		
Mean (SD)	0.11 (0.10)	0.09 (0.13)
Median (range)	0.09 (–0.02 to 0.36)	0.10 (–0.10 to 0.30)
Visual contrast sensitivity		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Intraocular pressure, mm Hg		
Mean (SD)	10.81 (1.97)	11.81 (2.51)
Median (range)	10.00 (8, 14)	11.00 (8 to 16)

Source: Clinical study report for the OCT-1 study.[16]

FAS = full analysis set; IVCM = in vivo confocal microscopy; logMAR = logarithm of the minimum angle of resolution; OCT = optical coherence tomography; OCT-1 = Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis; SD = standard deviation; VAS = visual analogue scale.

NOTE: N refers to number of eyes.

Interventions

During the 30-day run-in period, patients received treatment with CH 0.10% ophthalmic solution (identical to the control group study medication in the CHOC study). One drop of solution was instilled in each eye three to six times daily, according to the patient's accustomed dosage regimen.

During the treatment period, patients received viscous CH 0.55% ophthalmic solution (Cystadrops). After dispensing, the 5 mL vials were to be stored between 2°C and 8°C at night and at room temperature during the day and could be used for seven consecutive days. At the start of the treatment period, patients followed the same dosage regimen as in the run-in period. At each study visit, the number of instillations per day was adjusted according to the algorithm described in Table 23. Determination of the patient's status in the algorithm was based on ophthalmic assessments including IVCM total score.

There were no required or prohibited concomitant medications during the treatment period. Other ophthalmic formulations were allowed but could not be administered within 10 minutes of study drug instillation. Two patients (25%) took other ophthalmological medications before or during the study.

Patients (or parents) were to record adherence with study medication in a daily diary until month 24. Adherence was based on patient reporting at subsequent study visits.

Table 23: Dosage Adjustment Algorithm

Status According to Ophthalmic Assessments	Dosage Adjustment
Day 30 visit	
Worsening	Stop treatment
No change	No change in dosage
Improvement	Decrease by 1 instillation/day
Day 90 visit	
Worsening	Stop treatment or increase by 1 instillation/day
No change	Decrease by 1 instillation/day
Improvement	Decrease by 2 instillations/day
Day 180 to month 48 visits	
Worsening	Increase by 1 instillation/day
No change	No change in dosage
Improvement	Decrease by 1 instillation/day

Source: Clinical Study Report for the OCT-1 study.[16]

Efficacy Outcomes

Corneal Cystine Crystal Burden

The primary end point was the change from baseline (start of treatment period) to each subsequent visit. IVCM was performed and CCCS was assessed using the same methods at each study visit as in the CHOC study. CCCS was assessed by a single evaluator at all time points, except at the month 60 visit.

The depth of CCCDs was measured as a thickness in the central cornea was measured using the Heidelberg Retina Tomograph (IVCM) as well as optical coherence tomography

(OCT). A corneal pachymetry map was obtained with OCT at high resolution and crystal layer thickness was measured using the software-provided caliper.

Ocular Symptoms Related to Corneal Cystine Crystal Deposits

Photophobia was graded by the investigator on an ordinal scale of 0 to 5. The anchors for the investigator's photophobia scale were "absence of photophobia" (score of 0) and "extreme photophobia" (score of 5).

Vision-Related Function

Visual acuity on the logarithm of the minimum angle of resolution (logMAR) scale was assessed, with possible values ranging from –0.3 to +2.3. Lower values indicate better visual acuity.

Visual contrast sensitivity was assessed using a contrast sensitivity chart, with possible values ranging from –3.0 to +3.0. Lower values indicate better visual contrast sensitivity.

Complications of Corneal Cystine Crystal Deposits

Intraocular pressure (IOP) was measured using tonometry.

Safety Outcomes

Adverse Events

AEs and serious AEs (SAEs) were recorded with the exception of LADRs lasting for less than one hour. SAEs occurring up to 30 days following study completion were reported.

Notable Harms

Local adverse drug reactions

Patients (or parents) recorded the following information on specific LADRs in the daily diary following each instillation of study medication: time of instillation, the occurrence of local symptoms (redness, blurring, irritation, itching, burning, discomfort, and pain), local symptom duration, and the severity of each local symptom (mild, moderate, severe, or unbearable). After month 24, LADRs were no longer recorded daily and LADRs (along with their duration and severity) were reported only if patients considered them necessary to report.

Eye pain at instillation

At each assessment visit, pain was rated on a 100 mm visual analogue scale (VAS) and recorded by the ophthalmologist. The anchors of the scale were "no pain" at 0 and "worse pain ever" at 100 mm.

Statistical Analysis

All efficacy analyses were performed using the eye as the unit of analysis. A GEE model was used to analyze change in IVCM total score from baseline to each visit with each pair of eyes as a cluster. While these may have been intercept-only models (one for each post-baseline visit), it was not possible to determine the structure of the models. Sample size was based solely on what was considered to be a realistically obtainable sample.

Analysis Populations

The FA set was defined as all randomized patients (or eyes) that received at least one dose of study treatment and had a baseline assessment and at least one other assessment following the first dose of study treatment. Safety analyses were based on the safety set, which included all patients who received at least one dose of study treatment.

There were no major protocol deviations and most minor protocol deviations were associated with study visits occurring outside of the pre-specified time windows or incomplete written consent before study treatment or study extensions.

Patient Disposition

All eight patients remained in the study until the end at month 60. The FA and safety populations were identical.

Exposure to Study Treatments

Patient adherence to treatment, as assessed by daily dairy during the first 24 months of the treatment period, was [redacted] or higher for all patients during the first year of treatment with study medication (Table 24). The median adherence rate was [redacted] and higher during the first 18 months of treatment and was [redacted] during months 18 to 24 of treatment. Adherence rates ranged from as low as [redacted] during months 18 to 24 to as high as [redacted] during day 90 to month 9. There were no reported treatment interruptions or discontinuations. Treatment adherence information was not available beyond month 24.

One patient did not adhere to the dosage change at day 90 and instead received one extra instillation per day, leading to adherence rates of over [redacted].

Table 24: Treatment Exposure

	OCT-1 N = 8 FAS
Duration of treatment intake, months	
Mean (SD)	[redacted]
Median (range)	[redacted]
Number of daily instillations	
Day 1 to day 30	
Mean (SD)	[redacted]
Median (range)	[redacted]
Day 30 to day 90	
Mean (SD)	[redacted]
Median (range)	[redacted]
Day 90 to month 24	
Mean (SD)	[redacted]
Median (range)	[redacted]
Month 24 to month 42	
Mean (SD)	[redacted]
Median (range)	[redacted]
Month 42 to month 60	
Mean (SD)	[redacted]

	OCT-1 N = 8 FAS
Median (range)	[redacted]
Median adherence including days of interruption (range), %	
Day 1 to day 30	[redacted]
Day 30 to day 90	[redacted]
Day 90 to day 180	[redacted]
Day 180 to month 9	[redacted]
Month 9 to month 12	[redacted]
Month 12 to month 18	[redacted]
Month 18 to month 24	[redacted]

Source: Clinical Study Report for the OCT-1 study.[16]

FAS = full analysis set; OCT-1 = Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis; SD = standard deviation.

NOTE: N refers to number of patients.

Efficacy

Corneal Cystine Crystal Burden

In vivo confocal microscopy score (primary end point)

Change from baseline to day 180, the original treatment period, in mean IVCM total score was –2.75 (95% CI, –4.15 to –1.35). Overall, mean IVCM score decreased from baseline to day 90 and then remained constant throughout the rest of the 60-month treatment period (Table 25 and Figure 2). From baseline to month 60, 81.3% of eyes had a decreased score, 12.5% had no change, and 6.3% had an increased score.

The individual patient curves for IVCM total score over time (Figure 3) revealed that treatment response over time was heterogeneous. While seven patients initially experienced an improvement in IVCM total score of approximately 5 points, only five then maintained it or continued to improve over the 60-month period, while two patients instead experienced a steady increase in score and were close to the baseline score at month 60. One patient had an IVCM total score that fluctuated over the whole period.

Mean IVCM score by corneal layer show varying trends over time, depending on the layer (Figure 4). Mean IVCM score in the epithelium and basal epithelium were consistently low (approximately 1 or less) through the treatment period. There was a consistent decreasing trend in IVCM score over the whole period in the Bowman‘s layer, while the decreasing trend was consistent up to approximately month 24 in the superficial and medium stroma with an unclear trend following month 24. In the deep stroma, mean scores were consistently low (approximately 1 or less), but with a decreasing trend in the first 12 months and an increasing trend in the rest of the treatment period.

Corneal cystine crystal score

Mean CCCS followed a similar trend over time as to IVCM total score (Table 25), with a decrease from baseline to day 90 of 2.91 (SD of 0.13) to 2.78 (SD of 0.22) and values ranging from 2.73 to 2.81 following day 90 (with the exception of month 60, at which CCCS was rated by a different investigator).

Crystal layer thickness

Mean crystal layer thickness measured by IVCM tended to decrease over the entire 60-month treatment period, with a mean change from baseline to month 60 of [redacted].

Mean crystal layer thickness measured by OCT decreased substantially in the first nine months and then stayed within a small range from month 9 to month 48. There was a mean change from baseline to month 60 of –68.9 µm (SD of 34.1 µm).

Table 25: Corneal Cystine Crystal Burden

	OCT-1 N = 16 eyes FAS
IVCM total score (primary end point)	
Mean at baseline (SD)	11.38 (2.94)
Mean change from baseline (SD)	
Day 90	–3.19 (1.80)
Day 180	–2.75 (2.29)
Month 12	–3.25 (2.41)
Month 24	–3.50 (2.07)
Month 36	–3.88 (2.31)
Month 48	–3.19 (3.04)
Month 60	–3.44 (2.78)
Change category from baseline to month 60, n (%)	
Decrease	13 (81.3)
No change	2 (12.5)
Increase	1 (6.3)
Mean cystinosis corneal crystal score (SD)	
Baseline	2.91 (0.13)
Day 90	2.78 (0.22)
Day 180	2.75 (0.20)
Month 12	2.81 (0.21)
Month 24	2.75 (0.29)
Month 36	2.73 (0.32)
Month 48	2.75 (0.32)
Month 60[a]	1.88 (0.67)[a]
Crystal layer thickness by IVCM, µm	
Mean at baseline (SD)	[redacted]
Mean change from baseline (SD)	
Day 90	[redacted]
Day 180	[redacted]
Month 12	[redacted]
Month 24	[redacted]
Month 36	[redacted]
Month 48	[redacted]
Month 60	[redacted]
Crystal layer thickness by OCT, µm	
Mean at baseline (SD)	306.38 (98.87)

	OCT-1 N = 16 eyes FAS
Mean change from baseline (SD)	
Day 90	–27.2 (27.0)
Day 180	–20.8 (29.4)
Month 12	–35.0 (36.2)
Month 24	–47.3 (37.0)
Month 36	–39.8 (42.5)
Month 48	–41.3 (41.1)
Month 60	–68.9 (34.1)

Source: Clinical study report for the OCT-1 study.[16]

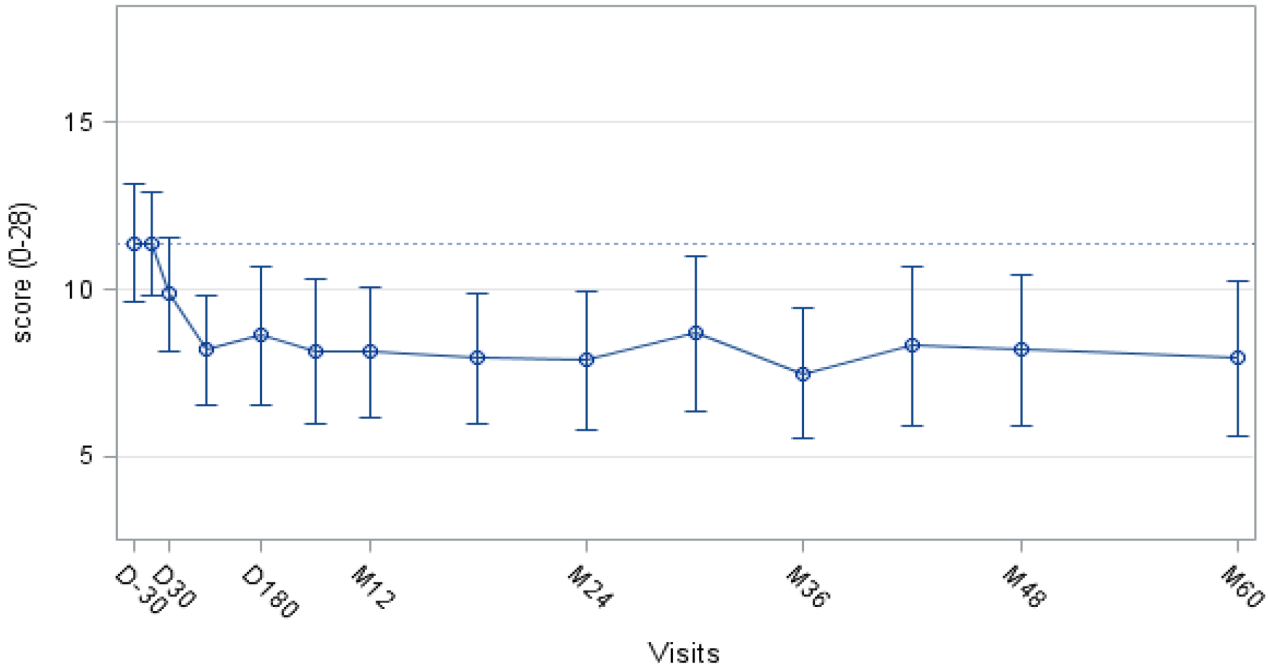
FAS = full analysis set; IVCM = in vivo confocal microscopy; OCT = optical coherence tomography; OCT-1 = Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis; SD = standard deviation.

NOTE: N refers to number of eyes.

NOTE: Baseline refers to the start of treatment with CH 0.50%.

[a] Cystinosis corneal crystal score was evaluated by one assessor up to month 48 and by a different assessor for the month 60 visit.

Figure 2: Mean IVCM Total Score at Each Study Visit



Source: Clinical Study Report for the OCT-1 study.[16]

D = day, IVCM = in vivo confocal microscopy; M = month.

NOTE: Unit of analysis is the eye (N = 16 eyes). Error bars indicate 95% confidence intervals. The second data point from the left corresponds with the baseline visit.

Figure 3: [redacted]

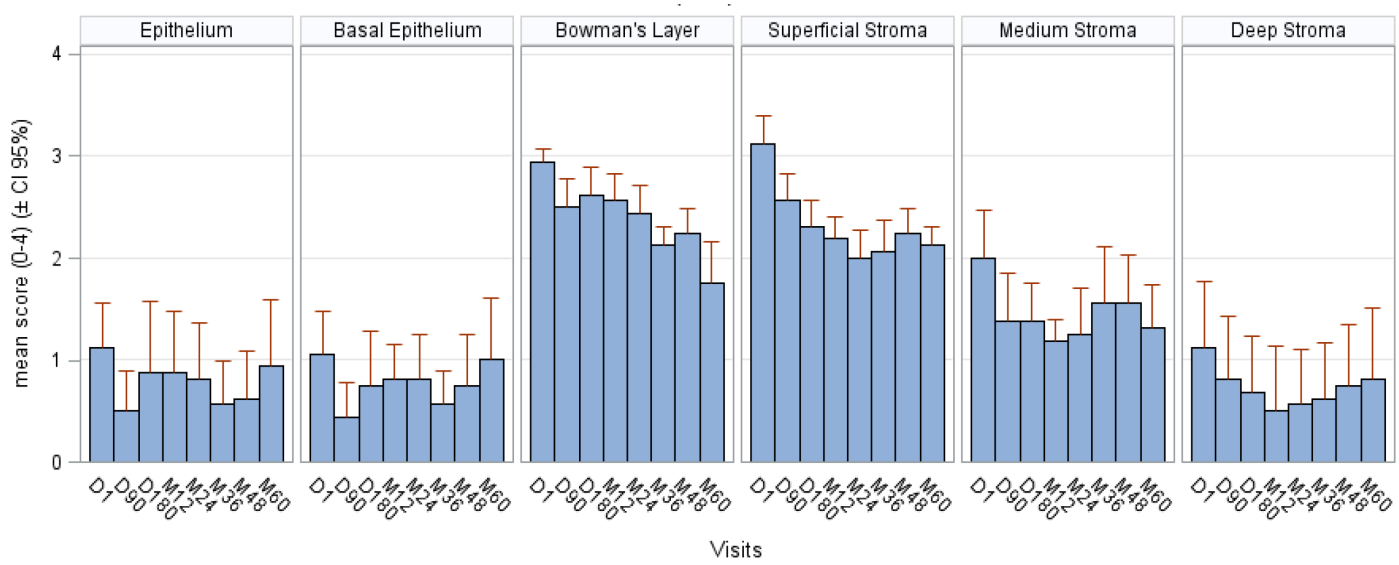
Confidential data removed at manufacturer's request.

[redacted]

D = day, IVCM = in vivo confocal microscopy; M = month.

NOTE: Dashed vertical lines indicate baseline visit.

Figure 4: IVCM Total Score by Layer at Each Study Visit



Source: Clinical Study Report for the OCT-1 study.[16]

CI = confidence interval; D = day, IVCM = in vivo confocal microscopy; M = month.

NOTE: Unit of analysis is the eye (N = 16 eyes). Error bars indicate 95% confidence intervals. Day 1 represents the baseline visit.

Ocular Symptoms Related to Corneal Cystine Crystal Deposits

Investigator-rated photophobia

Mean investigator-rated photophobia score decreased from baseline to month 60 by 0.9 points (SD of 1.3 points, Table 26 and Figure 5). However, there was substantial heterogeneity in treatment response between patients (Figure 6), with patients experiencing a mean change in photophobia score from baseline to month 60 ranging from an increase of 1 point to a decrease of 3 points (Table 26). Details on how photophobia score was determined on a per patient basis were not provided. Half of the patients had an improvement in photophobia score from baseline to month 60.

Table 26: Investigator-Rated Photophobia

	OCT-1 N = 16 eyes FAS
Photophobia rated by investigator	
Mean at baseline (SD)	2.50 (0.89)
Mean change from baseline (SD)	
Day 90	–0.5 (0.9)
Day 180	–0.3 (0.9)
Month 12	–0.3 (0.8)
Month 24	–1.0 (0.7)
Month 36	–1.1 (0.8)
Month 48	–0.9 (1.4)
Month 60	–0.9 (1.3)
Change category per patient from baseline to month 60, n (%)	
Improved by 3 points	[redacted]
Improved by 2 points	[redacted]
Improved by 1 point	[redacted]
No change	[redacted]
Worsened by 1 point	[redacted]

Source: Clinical Study Report for the OCT-1 study.[16]

FAS = full analysis set; OCT-1 = Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis; SD = standard deviation.

NOTE: N refers to number of eyes.

NOTE: Baseline refers to the start of treatment with CH 0.50%.

Figure 5: [redacted]

Confidential data removed at manufacturer's request.

[redacted]

D = day, IVCM = in vivo confocal microscopy; M = month.

NOTE: Unit of analysis is the eye (N = 16 eyes). Error bars indicate 95% confidence intervals (see the Statistical Analysis section). The second data point from the left corresponds with the baseline visit.

Figure 6: [redacted]

Confidential data removed at manufacturer's request.

[redacted]

D = day, M = month. NOTE: Dashed vertical lines indicate baseline visit.

Vision-related function

Visual acuity and contrast sensitivity did not notably change over the treatment period (Table 27).

Table 27: Vision-Related Function

	OCT-1 N = 16 eyes FAS
Mean best corrected visual acuity (SD), logMAR scale	
Baseline	0.09 (0.13)
Day 90	0.07 (0.10)
Day 180	0.10 (0.12)
Month 12	0.07 (0.12)
Month 24	0.14 (0.10)
Month 36	0.06 (0.11)
Month 48	0.02 (0.10)
Month 60	0.04 (0.10)
Mean contrast sensitivity (SD), vision contrast scale	
Baseline	[redacted]
Day 90	[redacted]
Day 180	[redacted]
Month 12	[redacted]
Month 24	[redacted]
Month 36	[redacted]
Month 48	[redacted]
Month 60	[redacted]

Source: Clinical Study Report for the OCT-1 study.[16]

FAS = full analysis set; IVCM = in vivo confocal microscopy; OCT = optical coherence tomography; OCT-1 = Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis; SD = standard deviation.

NOTE: N refers to number of eyes.

NOTE: Baseline refers to the start of treatment with CH 0.50%.

Complications of Corneal Cystine Crystal Deposits

Intraocular pressure

IOP tended to increase over the treatment period, though the mean increase was not notable compared with the SDs and expected daily fluctuations.

Table 28: Intraocular Pressure

	OCT-1 N = 16 eyes FAS/SS
Mean intraocular pressure (SD), mm Hg	
Baseline	11.81 (2.51)
Day 90	12.44 (1.79)
Day 180	11.50 (3.18)
Month 12	13.19 (2.07)
Month 24	14.69 (2.47)
Month 36	13.94 (2.17)
Month 48	14.75 (2.32)
Month 60	13.94 (4.17)

Source: Clinical Study Report for the OCT-1 study.[16]

Abbreviations: FAS = full analysis set; IVCM = in vivo confocal microscopy; OCT = optical coherence tomography; OCT-1 = Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis; SD = standard deviation; SS = safety set.

NOTE: N refers to number of eyes.

NOTE: Baseline refers to the start of treatment with CH 0.50%.

Safety

Adverse Events and Serious Adverse Events

AEs were reported in 87.5% of the patients and eye disorder AEs were reported in 25.0% of the patients (Table 29). Five eye disorders were reported by one patient each, and of these, corneal neovascularization and papilloedema were SAEs. Non-ocular SAEs occurring in more than one patient were epiphyseal surgery and knee deformity.

Withdrawal Due to Adverse Events and Deaths

There were no withdrawals due to AEs or deaths during the study.

Notable Harms

Local adverse drug reactions

LADRs during the first 24 months of the treatment period for which severity was reported are summarized in Table 29. All patients experienced at least one LADR, with the most common LADRs being eye pain / stinging (87.5% of patients), blurred vision (75.0%), and eye irritation / burning (50.0%). Abnormal sensation in eye, eye pruritus, and ocular discomfort occurred in two patients and all other LADRs occurred in one patient.

Severe eye irritation occurred in one patients and severe eye pain (stinging) occurred in two patients. Unbearable eye irritation and eye pain occurred in one patient each. There were two severe and three unbearable events of eye irritation (burning) and 21 severe and 37 unbearable events of eye pain (stinging) over the 24-month reporting period.

Severe LADRs lasted for one minute or less (median duration of 10 seconds) and unbearable LADRs lasted for three minutes or less (median duration of five seconds). All LADRs, regardless of severity, had a duration of three minutes or shorter.

The number of patients recording at least one LADR within a three-month time period decreased over the first 24 months of treatment from eight to two (Figure 7). Similarly, the number of LADRs reported in each three-month period steadily decreased.

During the run-in period three patients reported at least one LADR with instillation of CH 0.10%. All LADRs were either mild or moderate stinging and lasted two minutes or less.

Table 29: Adverse Events and Local Adverse Drug Reactions

	OCT-1 N = 8 Safety Set
AEs	
Patients with > 0 AEs, N (%)	7 (87.5)
Eye disorders	2 (25.0)
Chalazion	1 (12.5)
Corneal neovascularization	1 (12.5)
Dry eye	1 (12.5)
Hordeolum	1 (12.5)
Papilloedema	1 (12.5)
All other disorders occurring in > 1 patient	
Epiphyseal surgery	[redacted]
Gastroenteritis	[redacted]
Knee deformity	[redacted]
Nasopharyngitis	[redacted]
Vomiting	[redacted]
SAEs	
Patients with > 0 SAEs, N (%)	6 (75.0)
Eye disorders	
Corneal neovascularization	1 (12.5)
Papilloedema	1 (12.5)
All other disorders occurring in > 1 patient	
Epiphyseal surgery	[redacted]
Knee deformity	[redacted]
WDAEs	
WDAEs, N (%)	0
Deaths	
Number of deaths, N (%)	0
LADRs from baseline to month 24	
Patients with > 0 LADRs, N (%)	[redacted]
Abnormal sensation in eye	[redacted]
Eye irritation / burning	[redacted]
Eye irritation / irritation	[redacted]
Eye pain / stinging	[redacted]
Eye pruritus	[redacted]
Eyelid irritation	[redacted]
Lacrimation increased	[redacted]
Ocular discomfort	[redacted]
Ocular hyperemia	[redacted]
Blurred vision	[redacted]
Patients with > 0 severe LADRs, N (%)	[redacted]
Eye irritation / burning	[redacted]
Eye pain / stinging	[redacted]

	OCT-1 N = 8 Safety Set
Patients with > 0 unbearable LADRs, N (%)	[redacted]
Eye irritation / burning	[redacted]
Eye pain / stinging	[redacted]
Median duration of severe LADRs (range), seconds	[redacted]
Eye irritation / burning	[redacted]
Eye pain / stinging	[redacted]
Median duration of unbearable LADRs (range), seconds	[redacted]
Eye irritation / burning	[redacted]
Eye pain / stinging	[redacted]

Source: Clinical Study Report for the OCT-1 study.[16]

AE = adverse event; OCT-1 = Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis; LADR = local adverse drug reaction; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

NOTE: N refers to number of patients unless otherwise specified.

NOTE: LADRs with severities or durations not reported are not summarized in this table.

Figure 7: [redacted]

Confidential data removed at manufacturer's request.

[redacted]

LADR = local adverse drug reaction; M = month; Nb = number.

NOTE: Bars correspond to the total number of LADRs recorded for each period between study assessments. Line graph corresponds to the number of patients reporting any LADRs for each period.

Eye pain at instillation

Mean eye pain at instillation on a 100 mm VAS was minimal at baseline ([redacted]) and increased from baseline to days 90 and 180 to [redacted], respectively. Mean eye pain subsequently decreased over the rest of the treatment period. The maximum reported value for eye pain was [redacted] at day 90 and from months 30 to 60 the maximum reported value ranged from [redacted].

Table 30: Eye Pain at Instillation

	OCT-1 N = 16 eyes FAS/SS
Mean eye pain at instillation (SD), 0 to 100 mm visual analogue scale	
Mean at baseline (SD)	[redacted]
Mean change from baseline (SD)	
Day 90	[redacted]
Day 180	[redacted]
Month 12	[redacted]
Month 24	[redacted]
Month 36	[redacted]
Month 48	[redacted]
Month 60	[redacted]

Source: Clinical Study Report for the OCT-1 study.[16]

FAS = full analysis set; OCT-1 = Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis; SD = standard deviation; SS = safety set.

NOTE: N refers to number of eyes.

NOTE: Baseline refers to the start of treatment with CH 0.50%.

Limitations

The OCT-1 study was an OL, single-arm manufacturer-sponsored study and conclusions on the comparative efficacy and harms of Cystadrops versus best supportive care or another treatment for corneal cystine crystals could not be drawn. It was not possible draw conclusions about the change in IVCM total score from baseline as the GEE model structure was unclear, the time point for the primary analysis was unclear, and there was no statistical consideration for the multiple time points of evaluation. Statistical analyses were not available for any other outcomes.

According to the clinical experts consulted for this review, patient reporting of treatment adherence and LADRs may have become less reliable with time over the 24-month reporting period. Treatment adherence data were recorded for only the first 24 months of the 60-month treatment period and the available data revealed a wide range of adherence values per period.

Discussion

Efficacy

There was no control group in this study available for comparison. Overall, mean values for measures of crystal burden and photophobia demonstrated a numerical improvement from baseline to month 60. Measures of corneal crystal density (IVCM total score and CCCS) improved on average from baseline to day 90 and remained constant afterward. Mean investigator-rated photophobia also decreased from baseline to month 60, with most of the change occurring in the first 24 months. However, there was more variability over time in photophobia than in the measures of crystal burden. According to the clinical experts consulted for this review, some of this variability could have been modulated by the presence of other ocular problems commonly experienced in patients with cystinosis, such as allergies and dry eye.

Corneal crystals and photophobia were not completely eliminated in any of the patients and this may be due in part to the adaptive dosage algorithms. If a patient experienced improvement, they subsequently decreased their doses per day by one and may have therefore transitioned to a less efficacious dosage regimen. However, the clinical experts consulted for the review indicated that the dosage adjustment algorithms were reasonable and could be applied in clinical practice.

There was heterogeneity among patients with regard to IVCM total score and investigator-assessed photophobia over time. IVCM total score improved substantially in the first few months of treatment and then remained steady or decreased further in most patients. In two patients, there was a return back to baseline levels following an initial improvement. Four patients experienced an improvement in photophobia from baseline to month 60 while the others had no change or worsened by 1 point. Besides the already identified issues with these outcomes, it is possible that differences in treatment adherence between patients also contributed to the heterogeneity in response. Treatment adherence itself can be a complicated issue according to the clinical experts consulted for the review as it can be influenced by many factors, including AEs or the availability of a highly motivated caregiver.

There were no notable changes over the treatment period in visual acuity, visual contrast sensitivity, and IOP.

Harms

Two patients experienced AEs in the eye and there were two SAEs, corneal neovascularization and papilloedema. Of these, corneal neovascularization was of concern to the clinical experts consulted for the review. However, it is not possible to determine whether it was caused by the disease itself or by the study medication. There were no withdrawals due to AEs and no deaths during the study.

While all patients reported LADRs in the first three months of treatment, both the numbers of patients experiencing LADRs and the numbers of events decreased over the entire reporting period of 24 months. No LADRs lasted for more than three minutes and the only severe or unbearable LADRs were eye irritation (burning) and eye pain (stinging). Severe or unbearable burning and stinging occurred a total of five and 58 times, respectively. Long-term ocular symptoms from instillation were mostly of manageable severity and duration and decreased in frequency over time. While it is not possible to rule out the possibility that patient reporting became less reliable as the trial went on, the results suggest that LADRs either improved or were perceived to have improved over time.

Mean eye pain upon instillation, as suggested by the LADRs, was elevated during the first few months of treatment and decreased over the entire treatment period. The maximum value for eye pain corresponded with moderate pain for most of the first 30 months of treatment and then became milder.

Conclusion

No conclusions could be made on the safety profile of Cystadrops due to the limited sample size. Reporting of LADRs over the first 24 months of Cystadrops treatment suggested that LADRs improved in frequency and/or were perceived by patients to improve with longer durations of treatment. The efficacy results suggested that photophobia and corneal cystine crystal burden improved and that this improvement was maintained on average over the treatment duration of five years. However, the lack of a control group meant that conclusions could not be drawn regarding long-term efficacy of Cystadrops. There was a wide range in treatment adherence reported in the first 24 months of treatment as well as heterogeneity in each patient's long-term response to treatment as assessed by measures of corneal crystal burden and photophobia.

References

1. Elmonem MA, Veys KR, Soliman NA, van Dyck M, van den Heuvel LP, Levtchenko E. Cystinosis: a review. *Orphanet J Rare Dis.* 2016;11:47.
2. Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med.* 2002;347(2):111-121.
3. Ariceta G, Camacho JA, Fernandez-Obispo M, et al. Cystinosis in adult and adolescent patients: recommendations for the comprehensive care of cystinosis. *Nefrologia.* 2015;35(3):304-321.
4. Shams F, Livingstone I, Oladiwura D, Ramaesh K. Treatment of corneal cystine crystal accumulation in patients with cystinosis. *Clinical Ophthalmol.* 2014;8:2077-2084.
5. Tsilou E, Zhou M, Gahl W, Sieving PC, Chan CC. Ophthalmic manifestations and histopathology of infantile nephropathic cystinosis: report of a case and review of the literature. *Surv Ophthalmol.* 2007;52(1):97-105.
6. Cystadrops (cysteamine): 0.37% w/w ophthalmic solution [product monograph]. Toronto (ON): Recordati Rare Diseases Inc.; 2019 Feb 6.
7. Clinical Study Report: CHOC. Cysteamine hydrochloride for nephropathic cystinosis, open-label phase III pivotal study [CONFIDENTIAL internal manufacturer's report]. Puteaux (FR): Orphan Europe; 2013 Dec 10.
8. Cysteamine bitartrate (Procysbi): nephropathic cystinosis. *(CADTH Common drug review: patient input)*. Ottawa (ON): CADTH; 2017 Aug 1: https://cadth.ca/sites/default/files/cdr/relatedinfo/SR0526_Procysbi_Patient_Input.pdf. Accessed 2019 Feb 20.
9. De Braekeleer M. Hereditary disorders in Saguenay-Lac-St-Jean (Quebec, Canada). *Hum Hered.* 1991;41(3):141-146.
10. McGowan-Jordan J, Stoddard K, Podolsky L, et al. Molecular analysis of cystinosis: probable Irish origin of the most common French Canadian mutation. *Eur J Hum Genet.* 1999;7(6):671-678.
11. Rupar CA, Matsell D, Surry S, Siu V. A G339R mutation in the CTNS gene is a common cause of nephropathic cystinosis in the south western Ontario Amish Mennonite population. *J Med Genet.* 2001;38(9):615-616.
12. Liang H, Labbe A, Le Mouhaer J, Plisson C, Baudouin C. A new viscous cysteamine eye drops treatment for ophthalmic cystinosis: an open-label randomized comparative phase III pivotal study. *Invest Ophthalmol Vis Sci.* 2017;58(4):2275-2283.
13. Committee for Medicinal Products for Human Use. Assessment report: Cystadrops (mercaptamine). *(European public assessment report)*. London (GB): European Medicines Agency; 2016 Oct 13: https://www.ema.europa.eu/documents/assessment-report/cystadrops-epar-public-assessment-report_en.pdf. Accessed 2019 Feb 19.
14. Gahl WA, Kuehl EM, Iwata F, Lindblad A, Kaiser-Kupfer MI. Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eyedrops. *Mol Genet Metab.* 2000;71(1-2):100-120.
15. Labbe A, Baudouin C, Deschenes G, et al. A new gel formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis: the Cystadrops OCT-1 study. *Mol Genet Metab.* 2014;111(3):314-320.
16. Clinical Study Report: OCT-1. Adaptive dose regimen of cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis an open-label, dose-response pilot study “OCT-1” [CONFIDENTIAL internal manufacturer's report]. Puteaux (FR): Orphan Europe; 2014 May 06.
17. Liang H, Baudouin C, Tahiri Joutei Hassani R, Brignole-Baudouin F, Labbe A. Photophobia and corneal crystal density in nephropathic cystinosis: an in vivo confocal microscopy and anterior-segment optical coherence tomography study. *Invest Ophthalmol Vis Sci.* 2015;56(5):3218-3225.
18. Labbe A, Niaudet P, Loirat C, Charbit M, Guest G, Baudouin C. In vivo confocal microscopy and anterior segment optical coherence tomography analysis of the cornea in nephropathic cystinosis. *Ophthalmology.* 2009;116(5):870-876.
19. Petroll WM, Robertson DM. In vivo confocal microscopy of the cornea: new developments in image acquisition, reconstruction, and analysis using the HRT-Rostock Corneal Module. *Ocular surf.* 2015;13(3):187-203.
20. Keklikci U, Soker SI, Sakalar YB, Unlu K, Ozekinci S, Tunik S. Efficacy of topical cyclosporin A 0.05% in conjunctival impression cytology specimens and clinical findings of severe vernal keratoconjunctivitis in children. *Jpn J Ophthalmol.* 2008;52(5):357-362.