CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211302Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW NDA 211302 Class 2 Resubmission
CYSTADROPS (cysteamine ophthalmic solution) 0.37%

Application Type	NDA
Application Number(s)	211302
Submit Date(s)	February 28, 2020
Received Date(s)	February 28, 2020
PDUFA Goal Date	August 28, 2020
Division/Office	DDO/OSM
Reviewer Name(s)	Sonal D. Wadhwa
Review Completion Date	August 18, 2020
Established/Proper Name	Cysteamine ophthalmic solution
(Proposed) Trade Name	CYSTADROPS
Applicant	Recordati Rare Disease Inc.
Dosage Form(s)	Topical ophthalmic
Applicant Proposed Dosing Regimen(s)	One drop OU qid
Applicant Proposed Indication(s)/Population(s)	Treatment of corneal cystine crystal deposits in adults and children with cystinosis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of corneal cystine crystal deposits in adults and children with cystinosis

1. Summary

A Class 2 Resubmission of NDA 211302 was received on February 28, 2020, in response to the Agency Complete Response letter dated January 28, 2020:

- The facilities and controls used for, the manufacture, processing, packing, and holding of the drug product did not comply with the current good manufacturing practice (cGMP) regulations in 21 CFR 210 and 211.

- The methods to be used in, and the facilities and controls used for the manufacture, processing, packing and holding of the drug product were inadequate to preserve its identity, strength, quality, purity, stability or bioavailability.

CYSTADROPS is a cystine-depleting agent. It is a sterile viscous ophthalmic solution containing 5.6 mg/mL of cysteamine hydrochloride equivalent to 3.8 mg/mL of cysteamine (0.37%). Cystinosis is a rare and serious condition characterized by the intracellular accumulation of cystine. If not treated, cystinosis in its most severe form invariably leads to renal failure, necessitating dialysis and ultimately renal transplantation. Oral treatment with a cystine depleting agent, cysteamine, has greatly reduced the morbidity and mortality of this disease. Accumulation of cystine crystals due to cystinosis also occurs in the cornea. Due to the absence

of corneal vascularization, corneal cystine crystal deposits are minimally affected by systemic treatment with cysteamine.

Therefore, to treat the corneal crystal accumulation a topical treatment with a cysteamine containing eye drops is necessary to dissolve corneal cystine crystal deposits. If untreated topically, cystinosis can lead to the deterioration of visual capacity and eventually the need for a corneal graft.

The application for CYSTADROPS is submitted as a 505(b)(2) application listing Cystagon Capsules, NDA 20-392 as the listed drug product.

See the original Medical Officer's review in DARRTS dated 1/22/20.

The data contained in this application establishes the safety and efficacy of CYSTADROPS ophthalmic solution dosed qid for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.

2. Safety Update

On March 27, 2020, an updated Safety Report was provided with data for the reporting period from 01 November 2019 to 18 January 2020.

Cystadrops is currently licensed in 34 countries worldwide (28 European Union member states plus Canada, Columbia, Iceland, Liechtenstein, Mexico and Norway).

Severe eye irritation remains an important identified risk for Cystadrops. The important potential risks include punctate keratopathy and/or toxic ulcerative keratopathy, corneal neovascularization, ocular manifestations of Ehlers-Danlos like Syndrome, and increased risk of infection and medication error due to device assembly failure.

Review of the data collected during the reporting period and cumulative data does not reveal any new safety concerns that are not reflected in the current Risk Management Plan and prescribing information for Cystadrops; therefore, no changes to these documents are currently proposed.

The overall benefit-risk profile of Cystadrops remains favorable when the drug is used in its approved indication and duration of treatment.

Table 7: Cumulative sales of Cystadrops by region up to 18 January 2020

Region/Country	Quantity sold (b) (4)
Argentina	
Belarus	
Brazil	
Brunei Dar-es-S	
Columbia	
EU[a]	
Hong Kong	
Iceland	
India	
Japan	
Middle-East and North Africa[b]	
Norway	
Pakistan	
Russia	
Rwanda	
Serbia	
South Korea	
Uruguay	
Total	

EU=European Union.

[a] Including: Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Lithuania, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, the Netherlands and the UK.

[b] Including: Algeria, Bahrain, Egypt, Iraq, Israel, Jordan, Lebanon, Libya, Morocco, Oman, Qatar, Saudi Arabia, Syria, Tunisia, Turkey, and the United Arab Emirates.

3. Recommendations

NDA 211302 CYSTADROPS (cysteamine ophthalmic solution) 0.37% is recommended for approval for the treatment of corneal cystine crystal deposits in adults and children with cystinosis. There are no recommended post marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

4. Labeling

The agreed-upon labeling for NDA 211302 CYSTADROPS (cysteamine ophthalmic solution) 0.37% is attached.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SONAL D WADHWA
08/18/2020 03:51:55 PM

WILLIAM M BOYD
08/19/2020 06:29:46 AM

Deputy Division Director and Cross Discipline Team Leader Summary Review for Regulatory Action

Date	January 27, 2020
From	Wiley A. Chambers, M.D., and William . Boyd, M.D.
Subject	Deputy Division Director and Cross Discipline Team Leader Summary Review
NDA	211302
Applicant	Recordati Rare Disease Inc.
Date of Submission	3/28/19
PDUFA Goal Date	1/28/20
Proprietary Name	Cystadrops
Established or Proper Name	cysteamine ophthalmic solution, 0.37%
Dosage Form(s)	Topical ophthalmic solution
Recommended Indication(s)/Population(s)	Treatment of corneal cystine crystal deposits in adults and children with cystinosis
Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sonal Wadhwa
Statistical Review	Yan Wang,
Pharmacology Toxicology Review	Maria Rivera
OPQ Review Lead DP DS Facility Reviewer Biopharm Micro	Chunchun N. Zhang Yan Nang Sharon Kelly Steve Rhieu Mei Ou Jennifer Patro
CDTL Review	William M. Boyd
OSE/DMEPA	Nasim Roosta

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
CDTL=Cross-Discipline Team Leader
DMEPA=Division of Medication Error Prevention and Analysis

1. Summary

Cystadrops is a cystine-depleting agent. It is a sterile viscous ophthalmic solution containing 5.6 mg/mL of cysteamine hydrochloride equivalent to 3.8 mg/mL of cysteamine (0.37%). Cystinosis is a rare and serious condition characterized by the intracellular accumulation of cystine. If not treated, cystinosis in its most severe form invariably leads to renal failure,

necessitating dialysis and ultimately renal transplantation. Oral treatment with a cystine depleting agent, cysteamine, has greatly reduced the morbidity and mortality of this disease.

Accumulation of cystine crystals due to cystinosis also occurs in the cornea. Due to the absence of corneal vascularization, corneal cystine crystal deposits are minimally affected by systemic treatment with cysteamine. Therefore, to treat the corneal crystal accumulation a topical treatment with a cysteamine containing eye drops is necessary to dissolve corneal cystine crystal deposits. If untreated topically, cystinosis can lead to the deterioration of visual capacity and eventually the need for a corneal graft.

The application for Cystadrops is submitted as a 505(b)(2) application listing Cystagon Capsules, NDA 20-392 as the listed drug product.

2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of Cystadrops (cysteamine ophthalmic solution) 0.37% dosed qid to decrease corneal cystine crystal deposits in adults and children with cystinosis. Reductions in crystal deposits (crystals) is associated with decreased ocular symptoms.

Studies OCT-1 and CHOC demonstrate ability of Cystadrops to decrease corneal cystine crystal deposits. In Study OCT-1, the absolute mean number of crystals observed by In Vivo Confocal Microscopy (IVCM) from baseline was clinically reduced from month 6 through month 60. In Study CHOC, the absolute decrease from baseline in crystals observed by IVCM was clinically reduced at month 3.

The most common ocular adverse events after treatment with Cystadrops (incidence approximately 10% or greater) were: eye pain, vision blurred, eye irritation, ocular hyperemia, eye pruritus, lacrimation increased, deposit eye, and instillation site discomfort. Most of these events are also associated with the disease being treated.

The benefit of Cystadrops (cysteamine ophthalmic solution) 0.37% in decreasing corneal cystine crystal deposits outweighs the minimal risks to patients with Cystinosis.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cystinosis is a rare and serious condition characterized by the intracellular accumulation of cystine. Accumulation of cystine crystals due to cystinosis occurs also in the cornea. • Oral treatment with the cystine depleting agent, cysteamine, has greatly reduced the morbidity and mortality of this disease, but does not significantly reduce the formation of crystals in the cornea. • Direct topical treatment is necessary to dissolve corneal cystine crystal deposits and prevent serious ocular complications leading to the deterioration of visual capacity.	Without a topical cysteamine depleting medication patients with cystinosis will have a decrease in visual acuity and experience ocular pain.
Current Treatment Options	• There is currently one approved product in the United States for this indication which is Cystaran (cysteamine ophthalmic solution) 0.44%	Cystadrops will add another treatment option.
Benefit	• Cystadrops can be used less frequently (qid) than the currently approved Cystaran which is labeled q2h. The availability of multiple products reduces the chances of drug product shortages.	Cystadrops will add another treatment option.
Risk and Risk Management	• Cystadrops demonstrated a safety profile which was similar to Cystaran. • Labeling will identify the expected adverse reactions.	Routine monitoring and reporting of all adverse events are expected to be adequate.

3. Background

There is one approved product for this indication in the United States, Cystaran (cysteamine ophthalmic solution) 0.44% (NDA 200740). Cystaran was approved in 2012 and is approved for the treatment of corneal cystine crystal accumulation in patients with cystinosis. Its recommended dosage is one drop in each eye every 2 hours while awake.

Cystadrops was first approved for the treatment of corneal cystine crystal deposits by the European Commission in January 2017. Cystadrops is currently licensed in 31 countries worldwide (28 European Union EU member states plus Liechtenstein, Iceland and Norway).

Cystaran is stored by the patient in the freezer until use; it is then thawed and stored at room temperature for up to 7 days. Once thawed, it should not be refrozen. Cystadrops is stored by the patient in a refrigerator and after first opening is stored at room temperature for 7 days.

4. Product Quality

From the original Office of Product Quality Review dated 12/4/19:

The drug product Cystadrops is a clear and viscous ophthalmic solution and contains 3.8 mg of cysteamine (0.37%) equivalent to 5.6 mg/mL of cysteamine hydrochloride (0.55%). The drug product is packaged in a 10 mL (b) (4) amber (b) (4) glass vial with 5 mL fill volume and closed by a bromobutyl (b) (4) stopper 20 mm and sealed with a flip off tear off aluminum vial seal. An individually packed PVC dropper applicator with HDPE closure is supplied with each vial for the patient before the first use. All the excipients are compendial. As amended, the drug product specifications (release, regulatory and in-use) include tests for appearance, minimum fill, pH, viscosity, identity, assay, impurities, osmolality, sterility, and antimicrobial effectiveness. The specifications are acceptable. All analytical methods are described in reasonable detail and have been adequately validated.

DRUG SUBSTANCE

The active substance must correspond to the following requirements:

Test	Specifications	Analytical procedure
Appearance	White crystalline powder, with perceptible odour of hydrogen sulphide	Visual inspection
Identification test: IR spectrum HPLC retention time (b) (4)	The IR spectrum must be equivalent to the reference standard one The HPLC RT must be equivalent to the reference standard one Positive	USP <197K> USP <621> USP <191>
Appearance of solution	Clear and colourless	USP <631>
pH	(b) (4)	USP <791>
Water content	Not more than (b) (4) %	USP <921>
Sulfated Ash	Not more than (b) (4) %	USP <281>
HPLC Related Substances	(b) (4)	In-house method USP <621>
HPLC assay (on dry basis)		In-house method USP <621>
(b) (4) residual solvents		In-house method USP <621>

Source: Module 3.2.S.4.1 Specification

DRUG PRODUCT

Qualitative and quantitative composition of Cystadrops

Components	Formula (mg/mL)	Centesimal formula (w/w)	Function	Reference
Cysteamine* *As cysteamine hydrochloride*	3.8 mg *5.6 mg*	0.37 % *0.55 %*	Drug substance	In house (see 3.2.S.4)
Carmellose sodium ((b) (4))	[redacted]	[redacted] (b) (4)	Viscosity agent	Current NF, Ph. Eur. 0472 current ed.
Benzalkonium chloride	[redacted]	[redacted]	Antimicrobial preservative agent	Current NF, Ph. Eur. 0371 current ed.
Disodium edetate	[redacted]	[redacted]	[redacted] (b) (4)	Current USP, Ph. Eur. 0232 current ed.
Citric acid monohydrate	[redacted]	[redacted]	[redacted]	Current USP, Ph. Eur. 0456 current ed.
Sodium hydroxide	[redacted]	[redacted]	[redacted]	Current NF, Ph. Eur. 0677 current ed.
Hydrochloric acid (b) (4)	[redacted]	[redacted]	[redacted]	Current NF, Ph. Eur. 0002 current ed.
[redacted]	[redacted]	[redacted]	[redacted]	(b) (4)
Water for injections	[redacted]	[redacted]	[redacted]	Ph. Eur. 0169 current ed.

*Note: also known as mercaptamine.

Source: Module 3.2.P.1. Description and Composition of the Drug Product

Release and Regulatory Specifications of the Drug Product

TESTS	PROCEDURES	ACCEPTANCE CRITERIA (Release)	ACCEPTANCE CRITERIA (Regulatory)
GENERAL CHARACTERISTICS			
Appearance	Visual	Viscous limpid solution	Viscous limpid solution
TESTS			
pH	EP 2.2.3	(b) (4)	(b) (4)
Viscosity	EP 2.2.10	(b) (4) to (b) (4) mPas at 7s-1	(b) (4) to (b) (4) mPas at 7s-1
Osmolality	EP 2.2.35	(b) (4) to (b) (4) mOsm/kg	(b) (4) to (b) (4) mOsm/kg
Particulate Matter	USP <788>	≥ 10 µm NMT (b) (4) per vial ≥ 25 µm NMT (b) (4) per vial	≥ 10 µm NMT (b) (4) per vial ≥ 25 µm NMT (b) (4) per vial
Minimum fill	USP <755>	Mean: NLT (b) (4) mL Single vial: NLT (b) (4) mL	N/A
IDENTIFICATION			
Cysteamine hydrochloride	HPLC/UV	Positive	Positive
Disodium edetate	HPLC/UV	Positive	Positive
Benzalkonium chloride	HPLC/UV	Positive	Positive
ASSAY			
Cysteamine hydrochloride	HPLC/UV	(b) (4)	Shelf-life (stored in a glass vial closed by rubber stopper) (b) (4) In-Use (stored in a glass vial equipped with a dropper applicator) (b) (4)
Disodium edetate	HPLC/UV	(b) (4)	

Benzalkonium chloride	HPLC/UV	(b) (4)	
IMPURITIES			
(b) (4)	HPLC/UV	(b) (4)	
(b) (4)	HPLC/UV		
Any other impurity (each)	HPLC/UV		
Total degradation products			
MICROBIOLOGICAL CONTROL			
Sterility	EP 2.6.1	Sterile	Sterile
ANTIMICROBIAL ACTIVITY			
Antimicrobial effectiveness testing	USP <51>	N/A	Comply

Source: Module 3.2.P.5.1. Specifications

INSPECTIONS

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Recordati Industria Chimica e Farmaceutica SpA via Mediana Cisterna 4 , Aprilia, Campoverde, Italy, 4011	3002807989	Drug substance manufacturing and testing (release and stability) || 356h Status: Pending CSN	Approve - Based on Previous History
Baccinex SA Rue de la Source 3 , Courroux, n/a, Switzerland, 2822	3007272813	Manufacture and filling of drug product; sterility testing of drug product; || 356h Status: Pending SLQ	Withhold - Based on PAI
(b) (4)		-All quality control tests of the drug product, except the test for sterility (registration batches only) LCP	No Evaluation Necessary
		Manufacturer responsible for batch release of finished drug product || 356h Status: Pending SLQ	No Evaluation Necessary
		All quality control tests of the drug product, except the test for sterility; Storage of stability samples LCP, NEC	Approve - Based on Previous History

During a recent inspection of the Baccinex SA, FEI# 3007272813, manufacturing facility for this application, field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved if this site is continued to be included in the application.

Product Quality amendments submitted after November 23, 2019, were not reviewed as they were submitted late in the review cycle.

Per the original Office of Product Quality Review dated 12/4/19 for this application:

"The following Complete Response statements about the unacceptable manufacturing facility (Baccinex SA, FEI# 3007272813) should be included in the CR letter:

1. During a recent inspection of the Baccinex SA, FEI# 3007272813, manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. Regarding your response submitted on November 5, 2019, the following deficiencies remain unresolved as adequate data are not available for evaluation. In your resubmission, please address the following:

   a. Submit data required to demonstrate (b) (4)

[redacted] These parameters should be supported by development data and/or registration batch manufacturing data.

b. Clarify whether [redacted]

c. Revise your master batch record to reflect changes pertaining to [redacted]

The following Complete Response statements regarding unacceptable microbiology manufacturing deficencies should be included in the CR letter:

3. [redacted]

4. We also acknowledge that you intend to complete a [redacted] study prior to manufacture of Cystadrops commercial batches for the U.S. and that the study will simulate [redacted]. Provide successful results of this [redacted] simulation.

The following non-Complete Response comments should be included:

1. We acknowledge your revised drug specifications including a test for particulate matter. As you committed in the response dated on 11/22/2019, the Agency reminds you to provide the stability update with the particulate matter testing in the NDA resubmission.

2. The complete analytical method transfer report from [redacted] to [redacted] should be provided in the NDA resubmission."

Gramatical changes to the deficiencies will be made in the action letter.

5. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review dated 12/5/19:

This NDA is submitted as a 505(b)(2) application with Cystagon (cysteamine bitartrate) capsules as the listed drug. This NDA provides original nonclinical data in support of the ocular safety of Cystadrops and relies on the FDA's previous findings of safety and effectiveness for Cystagon to support the systemic safety. Published literature is also used as additional supportive information for ocular and systemic safety. The bridge for use of Cystagon as the listed drug is based on dose. The daily dose of cysteamine from Cystadrops (assuming 100% systemic absorption after ocular application) is no more than approximately 0.4% of the recommended daily oral Cystagon dose for the treatment of cystinosis in any age group.

Ocular toxicity studies were conducted in rabbits with Cystadrops at daily dosing frequencies of 3X, 4X, 6X, and 9X, with treatment duration up to 3 months. The key findings include:

- Conjunctival effects (redness, congestion, swelling, discharge and chemosis), corneal effects (opacity, vascularization and staining), and iritis. The incidence/severity of these generally increased as the frequency of administration increased from 3 to 9 instillations per day.
- Cystadrops 9X/day was not tolerated and required early sacrifice of the animals (2 weeks after study initiation). During clinical examinations on the day of necropsy, corneal opacities, right eye half opened, and right eye ruined were reported.
- Depending on the dosing frequency, microscopic findings were primarily observed in the limbus and cornea (inflammatory cells, strong dilated vessels, corneal neovascularization, thinned corneal epithelium, thinning/destruction of the limbus epithelium, keratic precipitates) and conjunctiva (extravasated lymphocytes and dilated vessels). More severe microscopic findings were observed at Cystadrops 9X/day (dilated vessels and dissociated collagen fibers in the conjunctiva, dissociated collagen fibers, neovascularization and stromal edema in the cornea).
- The NOAEL was Cystadrops 3X/day, the exposure margin is less than 1X for the intended clinical dosing regimen of Cystadrops 4X/day.
- Based on the observed adaptation with continuous treatment (i.e., findings reversed or decreased in incidence/severity with time), Cystadrops 4X/day was considered well tolerated. Therefore, the nonclinical results support the tolerability of the intended clinical dosing regimen of 4 drops daily.
- The vehicle had a significant contribution to the findings observed at a dosing frequency of 6X/day (only dosing frequency evaluated for the vehicle). Because the study did not include a 9X/day vehicle control group, the contribution of the vehicle to the findings observed in eyes treated with Cystadrops 9X/day is unknown.

Pharmacology/Toxicology recommends approval of the application.

6. Clinical Pharmacology

A Clinical Pharmacology review was not required for this application. All patients receiving Cystadrops are already on oral Cystagon Capsules for cystinosis. Due to the absence of corneal vascularization, corneal cystine crystal deposits are minimally affected by systemic treatment with cysteamine.

The Cystadrops application relies on the systemic safety of the listed drug Cystagon (cysteamine bitartrate) Capsules per 21 CFR 320.24(b)(6). The in vitro bridging between the clinical and commercial formulations has been established based on comparable pH, osmolality and viscosity values.

See the OPQ Integrated review dated 12/4/19, Chapter VI Biopharmaceutics.

7. Clinical Microbiology

This product is not an anti-infective.

8. Clinical/Statistical- Efficacy

From the original Clinical Review dated 1/22/20:

The two studies which provide the main support for safety and efficacy were: Study OCT-1 which enrolled 8 patients and Study CHOC which enrolled 32 patients. Both studies were conducted in France.

Study OCT-1: "Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis: An open-label, dose-response pilot study"

Primary Efficacy Endpoint

- Change in In Vivo Confocal Microscopy (IVCM) total score from baseline

The IVCM total score was a composite of the IVCM score for each of the 7 corneal layers; the presence of crystal deposits in each individual layer was graded on a scale from 0 to 4, so that the IVCM total score could range from 0 to 28. Higher scores designate larger amounts of crystal deposits; a decrease in IVCM total score indicates a reduction in corneal crystals in at least one layer of the cornea.

Study OCT-1: Primary Efficacy Endpoint (IVCM Score)

	Day 1	Day 30	Day 180	Month 12	Month 24	Month 36	Month 48	Month 60
IVCM total Score								
N	16	16	16	16	16	16	16	16
Mean (sd)	11.38	9.88	8.63	8.13	7.88	7.50	8.19	7.94
Min, Max	7, 18	5,16	5, 18	5, 12	3, 15	3, 14	5, 15	3, 15
Change From Baseline								
Mean (sd)	0	-1.50 (2.45)	-2.75 (2.29)	-3.25 (2.08)	-3.50 (2.07)	-3.88 (2.31)	-3.19 (3.04)	-3.44 (2.78)
P Value		0.0381	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Change From Baseline (%)								
Mean (sd)	0	-11.73% (25.09%)	-25.76% (18.63%)	-30.16% (16.87%)	-33.12% (20.83%)	-35.78% (21.57%)	-29.58% (25.37%)	-32.71 (25.40%)

The absolute mean change in IVCM total score from baseline was statistically significant at all time points.

Study CHOC: "Cysteamine Hydrochloride for nephrOpathic Cystinosis, open-label Phase 3 pivotal study"

Primary Efficacy Endpoint

- Total score of the corneal cystine crystal density measured by In-Vivo Confocal Microscopy (IVCM) in the 7 corneal layers. Scores were assessed by an independent masked reader

Study CHOC: Primary Efficacy Endpoint at Month 3 (IVCM Score)

	Cystadrops N=22	**CH 0.10% N=20**	**P value**
IVCM Score at Baseline			
Mean	10.6 (4.2)	10.8 (3.5)	
Absolute Change From Baseline in IVCM Score			
Mean	-4.60 (3.1)	-0.455 (3.4)	<0.0001
Min, Max	-11.0, -0.600	-7.60, 6.50	
Percent Change From Baseline			
Mean	-40.4% (16.0)	-0.679% (33.0)	

The absolute change from baseline in IVCM score compared between test drug and control was statistically significant at 3 months.

Cysteamine hydrochloride 0.10% eye drops is labeled to be given q2h while awake. In this trial it was only given qid; however, this was a superiority comparison not a noninferiority comparison, and it is acceptable that the product was not given as labeled.

The data contained in this submission establishes the efficacy of Cystadrops ophthalmic solution dosed qid for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.

9. Safety

From the original Clinical Review dated 1/22/20:

The main support for safety is from 2 clinical studies (Studies OCT-1 and CHOC) and the reference to Agency's finding of safety for NDA 20-392 Cystagon Capsules. Study OCT-1 enrolled 8 patients and had a duration of 5 years. Study CHOC enrolled 32 patients and had a duration of 3 months.

Demographics: Study OCT-1

Gender	Cystadrops N=8
Male	2
Female	6
Age (years) At Time of Inclusion	
Mean (sd)	12.1 (4.6)
Min, Max	7, 21

Demographics: Study CHOC

Gender	Cystadrops N=15	CH 0.10% N=16
Male	7	8
Female	8	8
Age (years) At Time of Inclusion		
Mean (sd)	19.2 (15.5)	15.1 (10.3)
Min, Max	2.8, 62.6	3.5, 36.0

Treatment Compliance/Exposure

Study OCT-1: Compliance (N=8)

	Instillations Prescribed-Mean	Instillations Administered-Mean
Day 1-30	4.0 (0.53)	4.0 (0.53)
Day 30-90	3.9 (0.83)	3.9 (0.83)
Day 90-180	2.9 (0.83)	3.0 (0.93)
Month 9-12	2.9 (0.83)	3.0 (0.93)
Month 12-18	2.9 (0.83)	3.0 (0.93)
Month 18-24	2.9 (0.83)	3.0 (0.93)
Month 24-30	2.8 (0.71)	2.9 (0.83)
Month 30-36	2.9 (0.83)	2.9 (0.83)
Month 36-42	2.9 (0.83)	2.9 (0.83)
Month 42-48	3.0 (1.07)	3.0 (1.07)
Month 48-60	3.0 (1.07)	3.0 (1.07)

Study CHOC: Treatment Exposure

	Cystadrops N=15	CH 0.10% N=16
Duration of Treatment (Days)		
Mean	86.3 (19.9)	92.7 (5.46)
Total Number of Instillations*		
Mean	316 (83.9)	370 (89.5)

*The theoretical duration of treatment was between 86 and 94 days, with a dose regimen of 4 drops per day for a theoretical total of 344 to 376 instillations.

Deaths

There were no deaths reported in either study.

Treatment Emergent Adverse Events

Study OCT-1: Treatment Emergent Adverse Events

System Organ Class	Number of Events
Eye disorders	5
Infections and infections	8
Surgical and medical procedures	12
Musculoskeletal disorders	7
Nervous system disorders	8
Renal and urinary disorders	2
GI disorders	3
Immune system disorders	4
Injury, poisoning, and procedural complications	4
Investigations	5
Metabolism disorders	7
Ear disorders	1
Reproductive disorders	1
Skin disorders	1
Social circumstances	1
Blood disorders	2

Study OCT-1: Ocular Treatment Emergent Adverse Events

	Number of Events
Chalazion	1
Corneal neovascularization	0
Dry eye	0
Hordeolum	1
Papilledema	1

Study CHOC: Treatment Emergent Adverse Events

System Organ Class	Number of Events Cystadrops N=15	Number of Events CH 0.10% N=16
Eye disorders	31	57
Infections and infections	7	6
Respiratory disorders	1	2
Nervous system disorders	3	0
General disorders	2	0
Injury, poisoning, and procedural complications	1	1
Metabolism disorders	1	1
Musculoskeletal disorders	2	0
Investigations	2	0
Ear disorders	1	0
GI disorders	1	0
Immune system disorders	1	0
Renal disorders	1	0
Skin disorders	0	1
Social circumstances	1	
Vascular disorders	0	1

Serious Adverse Events

Study OCT-1
Six patients experienced a total of 48 SAEs; of these, 46 were hospitalizations related to the underlying cystinosis disease and not to the topical administration of Cystadrops. Of the 2 remaining SAEs, 1 (corneal neovascularization) was reported as medically significant and 1 (knee deformity) was reported as persistent or significant disability/incapacity.

Study CHOC
Four patients reported 4 SAEs, two cases of gastroenteritis, one case of tiredness and one case of a corneal graft rejection.

Periodic Safety Update Report (PSUR)

Per the Periodic Safety Update Report (PSUR) covering 19 July 2018 to 18 January 2019:

No safety signals were newly identified, ongoing or closed during the reporting period. A summary of the safety concerns for Cystadrops at the beginning of the reporting period for this PSUR is presented in Table 8.

Table 8: Summary of safety concerns

Important identified risks	• Severe eye irritation
Important potential risks	• Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) • Corneal neovascularisation • Ocular manifestations of Ehlers-Danlos like syndrome (EDLS) • Increased risk of infection and medication error due to device assembly failure
Missing information	• Patients with other ocular co-morbidities • Patients receiving concomitant treatment with ophthalmic products containing BAK • Long-term safety

BAK=Benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome.
Source: Cystadrops Risk Management Plan (RMP) Version 1.3 (dated 30 September 2015), Module SVIII, Table 14.

The data contained in this submission establishes the safety of Cystadrops ophthalmic solution dosed qid for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.

10. Advisory Committee Meeting

No Advisory Committee Meeting was held for this application. There were no issues that were thought to benefit from a discussion at an advisory committee meeting.

11. Pediatrics

This product triggers PREA with a new dosing regimen. There is an agreed Pediatric Study Plan (PSP) under IND 140943 which includes a deferral of a pediatric study. The study will include children 0 months to 2 years old. The Pediatric Review Committee discussed and concurred with the plan on 12/17/2019.

Timelines:

- Estimated protocol submission date: No later than February 4, 2019
- Estimated study initiation date: No later than March 31, 2019
- Estimated study completion date: No later than December 31, 2021
- Estimated final report submission date: No later than June 30, 2022

12. Other Relevant Regulatory Issues

BIOSTATISTICS
From the original Biostatistics Review dated 11/18/19:

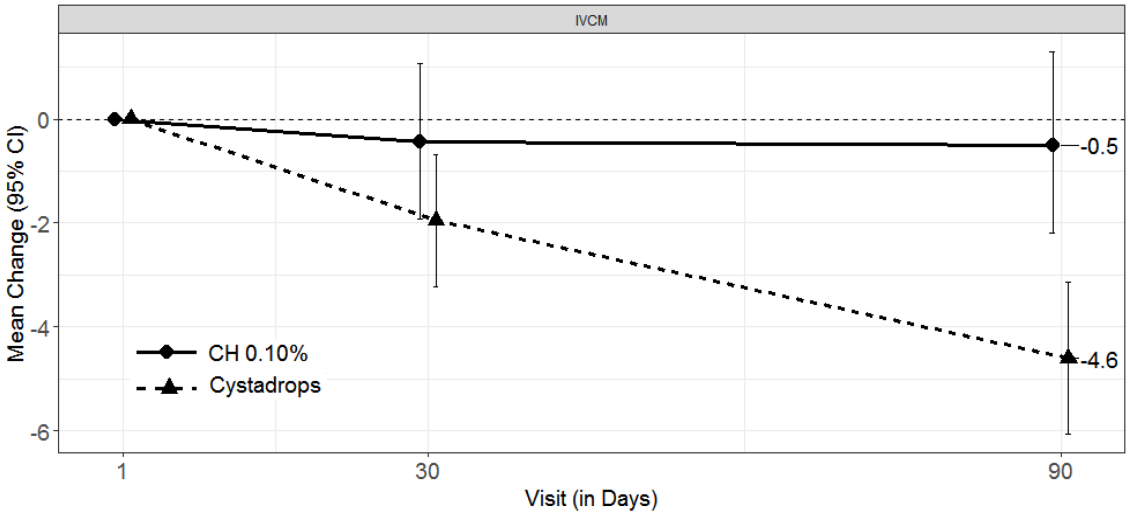
The OCT-1 study was an open-label adaptive, dose-response Phase 1/2a study. This study enrolled 8 subjects (16 eyes) aged from 7 to 21 years to receive Cystadrops up to five years. Cystadrops was instilled 3-5 times per day for the initial month (average 4 instillations). The dose regimen was then adapted to efficacy results at study visits (Months 1, 3, 6, 9, 12, and subsequently every 6 months until Month 48). On average, Cystadrops was instilled 3 times per day from Month 1 onward.

The CHOC study was a 3-month, open-label, randomized, multi-center, active-controlled Phase 3 study designed to demonstrate superiority of Cystadrops to the standard of care in France (Cysteamine hydrochloride eye drops solution 0,10% [CH 0.10%]) in reducing corneal cystine crystal deposits. In this study, a total of 32 subjects (64 eyes) at least 2 years of age with corneal cystine crystal deposits were randomized to either Cystadrops or CH 0.10%. Subjects were to receive one instillation of topical eye drops four times per day for 90 days in both eyes. During the treatment period, subjects had scheduled visits at Days 1, 30, 60 (Phone call), and 90.

In both studies, key efficacy evaluations were assessed based on: (i) corneal cystine crystal density as measured by In Vivo Confocal Microscopy (IVCM), (ii) using corneal cystine crystal score (CCCS) during slit lamp examination, (iii) photophobia (assessed by the investigator during slit-lamp examination), and (iv) crystal thickness (CT) in both eyes. The IVCM score provided a quantitative evaluation of the cystine crystals in seven layers of the cornea through multiple images where each layer was scored in 0-4 scale. The total IVCM score was a composite score of the scores attributed to each layer (range 0-28). CCCS was scored in a 0-3 scale in 0.25 increments and Photophobia was assessed on a 0-5 scale based on an objective assessment by the investigator.

In the pivotal Phase 3 study (CHOC), Cystadrops treated eyes demonstrated substantial reduction in the primary efficacy variable of corneal cystine crystal density (as measured by IVCM) from baseline throughout the study compared to CH 0.10% treated eyes. In this study, Cystadrops treated eyes yielded an average reduction of 4.6-unit in the total IVCM from baseline at Day 90 compared to a mean reduction of 0.5-unit in the CH 0.10% treated eyes (Figure 1). The treatment difference (*Cystadrops minus CH 0.10%*) in the mean reduction in the total IVCM score at Day 90 was 3.84 (95% CI: (2.11, 5.58); p-value < 0.001).
Also, Cystadrops treated eyes demonstrated significant reduction in the secondary efficacy variables of CCCS, CT, and photophobia compared to CH 0.10% treated eyes. For example, 30% and 47% of Cystadrops treated eyes demonstrated at least 1-unit improvement in CCCS and in photophobia from baseline at Day 90, respectively, compared to 0% and 6% of CH 0.10% treated eyes.

Figure 1: Mean change in total IVCM score from baseline over time
(Full Analysis Set)



Source: Appendix Table 8

The single arm study OCT-1 provided supporting evidence for the primary and secondary efficacy findings in the CHOC study. Also, most of the published literatures provided supportive evidence regarding the treatment benefit of topical application of cysteamine in improving corneal crystals density and photophobia.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)

No OSI consult was requested and no audit completed. Both studies were performed in France, and it was determined that the foreign data submitted could be relied upon without the need for an inspection.

FINANCIAL DISCLOSURE

Covered Clinical Study (Name and/or Number): OCT-1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 8		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator in Sponsor: Not applicable		

Covered Clinical Study (Name and/or Number): CHOC

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable		

Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator in Sponsor: Not applicable

PATIENT EXPERIENCE DATA RELEVANT TO THIS APPLICATION

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Sec 6.1 Study endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

OPDP

The Office of Prescription Drug Promotion (OPDP) did not complete a review of the submitted labeling since there was no substantially complete labeling developed during this review cycle.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, CYSTADROPS, and granted conditional acceptance on 6/21/19.

DMEPA completed a labeling review of the originally submitted USPI and carton/container labeling on 12/6/19.

13. Labeling

Incomplete, draft labeling for this application is located in the original Clinical Review dated 1/22/20; additional requests for information from the applicant will necessitate revision to this labeling. The Agency will continue to work with the applicant on labeling. The current draft labeling should not be transmitted to the applicant.

14. Recommended Comments to the Applicant

NDA 211302 Cystadrops (cysteamine ophthalmic solution) 0.37% will not be approved.

1. The facilities and controls used for, the manufacture, processing, packing, and holding of the drug product do not comply with the current good manufacturiung pactice (cGMP) regulations in 21 CFR 210 and 211. Specifically, during a recent inspection of the Baccinex SA, FEI# 3007272813, a manufacturing facility for this application, the Agency's field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required if this facility remains in the application. All submitted facilities must be in compliance with current Good Manufacturing Practices (cGMP) before this application may be approved.

2. The methods to be used in, and the facilities and controls used for the manufacture, processing, packing and holding of the drug product are inadequate to preserve its identity, strength, quality, purity, stability or bioavailability. Specifically,

   a. Regarding the response submitted on November 5, 2019, the following deficiencies remain unresolved as adequate data are not available for evaluation. In your resubmission, please:

      i. Submit data to demonstrate that (b) (4)

[redacted] These parameters should be supported by development data and/or registration batch manufacturing data.

ii. Clarify whether [redacted]

iii. Revise your master batch record to reflect changes pertaining to [redacted]

b. [redacted]

c. We also acknowledge that you intend to complete a [redacted] study prior to manufacture of Cystadrops commercial batches for the U.S. and that the study will simulate [redacted]. Please provide the results of this [redacted] simulation.

Although not a reason for the Complete Response, the following additional information is requested:

1. We acknowledge your revised drug specifications including a test for particulate matter. Please provide a stability update with the particulate matter testing in the NDA resubmission.

2. Please provide the complete analytical method transfer report from [redacted] to [redacted] in the NDA resubmission.

Amendments submitted to the NDA after November 23, 2019, were not reviewed as they were submitted late in the review cycle.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
01/27/2020 04:27:28 PM

WILEY A CHAMBERS
01/28/2020 07:43:42 AM

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	211302
Priority or Standard	Standard
Submit Date(s)	3/28/19
Received Date(s)	3/28/19
PDUFA Goal Date	1/28/19
Division/Office	DTOP/OND
Reviewer Name(s)	Sonal D. Wadhwa
Review Completion Date	11/22/19
Established/Proper Name	Cysteamine ophthalmic solution
(Proposed) Trade Name	Cystadrops
Applicant	Recordati Rare Disease Inc.
Dosage Form(s)	Topical ophthalmic
Applicant Proposed Dosing Regimen(s)	One drop OU qid
Applicant Proposed Indication(s)/Population(s)	Treatment of corneal cystine crystal deposits in adults and children with cystinosis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of corneal cystine crystal deposits in adults and children with cystinosis

Table of Contents

Glossary

AC	advisory committee
AE	adverse event
BPCA	Best Pharmaceuticals for Children Act
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Cystadrops is a cystine-depleting agent. It is a sterile viscous ophthalmic solution containing 5.6 mg/mL of cysteamine hydrochloride equivalent to 3.8 mg/mL of cysteamine (0.37%). Cystinosis is a rare and serious condition characterized by the intracellular accumulation of cystine. If not treated, cystinosis in its most severe form invariably leads to renal failure, necessitating dialysis and ultimately renal transplantation. Oral treatment with a cystine depleting agent, cysteamine, has greatly reduced the morbidity and mortality of this disease.

Accumulation of cystine crystals due to cystinosis also occurs in the cornea. Due to the absence of corneal vascularization, corneal cystine crystal deposits are minimally affected by systemic treatment with cysteamine. Therefore, to treat the corneal crystal accumulation a topical treatment with a cysteamine containing eye drops is necessary to dissolve corneal cystine crystal deposits. If untreated topically, cystinosis can lead to the deterioration of visual capacity and eventually the need for a corneal graft.

The application for Cystadrops is submitted as a 505(b)(2) application listing Cystagon Capsules, NDA 20-392 as the listed drug product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 211302 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of Cystadrops for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of Cystadrops (cysteamine ophthalmic solution) 0.37% dosed qid to decrease corneal cystine crystal deposits in adults and children with cystinosis. Reductions in crystal deposits (crystals) is associated with decreased ocular symptoms.

Studies OCT-1 and CHOC demonstrate ability of Cystadrops to decrease corneal cystine crystal deposits. In Study OCT-1, the absolute mean number of crystals observed by In Vivo Confocal Microscopy (IVCM) from baseline was clinically reduced from month 6 through month 60. In Study CHOC, the absolute decrease from baseline in crystals observed by IVCM was clinically reduced at month 3.

The most common ocular adverse events after treatment with Cystadrops (incidence approximately 10% or greater) were: eye pain, vision blurred, eye irritation, ocular hyperemia, eye pruritus, lacrimation increased, deposit eye, and instillation site discomfort. Most of these events are also associated with the disease being treated.

The benefit of Cystadrops (cysteamine ophthalmic solution) 0.37% in decreasing corneal cystine crystal deposits outweighs the minimal risks to patients with Cystinosis.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cystinosis is a rare and serious condition characterized by the intracellular accumulation of cystine. Accumulation of cystine crystals due to cystinosis occurs also in the cornea. • Oral treatment with the cystine depleting agent, cysteamine, has greatly reduced the morbidity and mortality of this disease, but does not significantly reduce the formation of crystals in the cornea. • Direct topical treatment is necessary to dissolve corneal cystine crystal deposits and prevent serious ocular complications leading to the deterioration of visual capacity.	Without a topical cysteamine depleting medication patients with cystinosis will have a decrease in visual acuity and experience ocular pain.
Current Treatment Options	• There is currently one approved product in the United States for this indication which is Cystaran (cysteamine ophthalmic solution) 0.44%	Cystadrops will add another treatment option.
Benefit	• Cystadrops can be used less frequently (qid) than the currently approved Cystaran which is labeled q2h. The availability of multiple products reduces the chances of drug product shortages.	Cystadrops will add another treatment option.
Risk and Risk Management	• Cystadrops demonstrated a safety profile which was similar to Cystaran. • Labeling will identify the expected adverse reactions.	Routine monitoring and reporting of all adverse events are expected to be adequate.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Sec 6.1 Study endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

See Section 1.1.

2.2. Analysis of Current Treatment Options

There is one approved product for this indication in the United States, Cystaran (cysteamine ophthalmic solution) 0.44% (NDA 200-740). Cystaran is stored in the freezer until use. Thawed and then stored at room temperature for up to 7 days. Once thawed, it should not be refrozen. Cystadrops is stored in a refrigerator and after first opening is stored at room temperature for 7 days.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cystaran (cysteamine ophthalmic solution) 0.44% (NDA 200740) was approved in 2012. It is approved for the treatment of corneal cystine crystal accumulation in patients with cystinosis. Its recommended dosage is one drop in each eye every 2 hours while awake.

3.2. Summary of Pre-submission/Submission Regulatory Activity

There was a Pre-NDA meeting on 5/15/18.

3.3. Foreign Regulatory Actions and Marketing History

Cystadrops was first approved for the treatment of corneal cystine crystal deposits by the European Commission in January 2017. Cystadrops is currently licensed in 31 countries worldwide (28 European Union EU member states plus Liechtenstein, Iceland and Norway).

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No OSI consult was performed as both studies were performed in France and it was determined that the data can be relied upon without the need for an inspection.

4.2. Product Quality

The final CMC review is pending. See CDTL review for complete findings.

4.3. Clinical Microbiology

This product is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

The final non-clinical pharmacology/toxicology review is pending. See CDTL review for complete findings.

4.5. Clinical Pharmacology

The final CMC review is pending. See CDTL review for complete findings.

4.6. Devices and Companion Diagnostic Issues

Not applicable. There is not a companion device or diagnostic.

4.7. Consumer Study Reviews

Not applicable. No consumer studies were conducted.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The table below lists the clinical studies that were reviewed to evaluate safety and efficacy of Cystadrops.

Study Name	Study Design	Test Product	Number of Subjects	Duration of Treatment	Study Status
OCT-1	Open-label, single-group trial	Run-in period: usual treatment with cysteamine hydrochloride 0.10% eye drops (CH 0.10%) (allowed: 3 – 6 instillations/eye per day). Treatment period: treatment with CYSTADROPS was initiated at the same dosing frequency as the run-in period dosing. Dose adaptation up to Month 48.	8	60 months	Complete
CHOC	Open-label, randomized, comparative trial	The study had 2 parallel treatment arms: Cystadrops and CH 0.10%. Both were given 4 instillations/eye/day for a period of 90 days	32	3 months	Complete

5.1. Review Strategy

The sources of clinical data utilized in this review include the studies listed in section 5.1. The two studies which provide the main support for safety and efficacy were: Study OCT-1 which enrolled 8 patients and Study CHOC which enrolled 32 patients. Both studies were conducted in France.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. OCT-1 and CHOC

6.1.1. Study OCT

Study OCT-1: "Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis: An open-label, dose-response pilot study"

Primary Objective: To establish the safety of Cystadrops (cysteamine hydrochloride 0.55%) along the treatment over a defined period

Secondary Objective:

- To find the lowest effective dose according to an empiric adaptive dose regimen algorithm
- To evaluate the response to Cystadrops treatment at defined period

Trial Design

This study was an open label dose-response controlled phase1/2a pilot study. Each patient was considered as his/her own control (with regards to the dose regimen frequency under their usual cysteamine eye drops formulation during a one-month run-in period). Eight pediatric or adult cystinosis patients of both genders, presenting with corneal cystine crystal deposits, regularly receiving the French hospital preparation of topical cysteamine, to which there was a documented good compliance at the time of the inclusion into the study, were recruited.

During the run-in period, topical cysteamine (i.e., cysteamine hydrochloride 0.10% eye drops referred to as "CH 0.10%") was instilled as usual, with at least three instillations per day. After the run-in period, Cystadrops (cysteamine hydrochloride 0.55%) was applied with the same daily frequency as the CH 0.10% solution. The dose regimen was adapted based on efficacy/response results (ophthalmology/clinical evaluations) at Day 30, Day 90, Day 180, Month 9, Month 12 and subsequently every 6 months up to Month 48. In the absence of safety signals, the per-protocol follow-up initially planned for 6 months was amended, extending the follow-up period to a total of 60 months.

Inclusion Criteria

- Male or female patients
- Aged from 3 years
- Having freely given their written informed consent to participate in the study. For patients aged less than 18 years consent will be obtained from the two parents
- Diagnosis of cystinosis based on a previous leukocyte cystine concentration > 1.5 nmoles half-cystine per mg protein
- Presence of corneal crystal deposits attested during a slit-lamp examination within 3 months prior to inclusion
- Treatment with cysteamine (CH 0.10%") reference topical formulation since at least 1 month
- Ability to comply with the eyewash regimen of 3 to 6 instillations daily
- Agreement to attend the Ophthalmic Core Laboratory for a total of 16 assessment visits within 60 months

Exclusion Criteria

- Patients with uncontrolled hepatic disorder, cardiovascular disease, neurologic disease, or cancer
- Laboratory tests out of normal range according to the reference laboratory values.

- Deviations may be accepted if the investigator considers that they are not clinically significant for the conduct of study
- Patients with history or presence of alcohol abuse or drug addiction
- Pregnant or breast-feeding women
- Women of child-bearing potential without effective contraception
- Patients likely to be non-compliant to the study procedure or for whom a long-term follow-up seems to be difficult to achieve

Treatments administered
The initial run-in period reference treatment was the patient's usual cysteamine hydrochloride 0.10% eye drops solution supplied by AGEPS. It was instilled 3 to 6 times per day, according to the usual daily fixed dose which was specific for each patient. The investigational product, cysteamine hydrochloride 0.55% viscous eye drops solution (Cystadrops) was provided in vials containing 5 ml of viscous eye drops solution and was supplied by Orphan Europe. Cystadrops was to be stored at -20°C before dispensing. After dispensing, it was to be stored in the refrigerator. When open, vials were stored in the refrigerator during the night and at room temperature during the day; by following these instructions, Cystadrops could be used for 7 consecutive days.

Selection of doses in the study
During the run-in period, topical cysteamine (CH 0.10%) was instilled as usual, with at least 3 and up to 6 instillations/eye/day. After the run-in period, Cystadrops was instilled according to the same schedule, and the dose regimen was adapted to ocular findings at Day 30, Day 90, Day 180, Month 9, Month 12 and subsequently every 6 months until Month 48.

Selection and timing of dose for each patient
The Cystadrops dose regimen was adapted according to the schemas presented in Figure 1 at Day 30, Figure 2 at Day 90 and Figure 3 from Day 180 to Month 48. As a rule, an improvement in ocular findings was to lead to a decrease in the number of instillations per day, whereas a worsening of ocular findings was to lead to the interruption of treatment (at Day 30 or Day 90) or to an increase in the number of instillations (from Day 90 onwards).

Investigational product, dose and mode of administration, batch number:
Cystadrops: cysteamine hydrochloride 0.55% viscous eye drops solution

- Route of administration: ocular use
- Dosage: initial treatment with at least 3 instillations per day. The dose regimen was adapted to ocular findings at Day 30, Day 90, Day 180, Month 9, Month 12 and subsequently every 6 months until Month 48.
- Batch numbers: 0739708059, 0739708080, 0739708147, 0739708245, 0739708331, 0739709040, 0739709231, 0739710039, 0739710189, 0739711046, 0739711234, 0739712040 and 0739712118.
- Duration of treatment: 60 months

Control product: Cysteamine hydrochloride 0.10% (powder and solvent for eye drops)

- Supplied by AGEPS, AP-HP
- Route of administration: ocular use
- Dosage: usual regimen

Figure 1 - Dose regimen algorithm at Day 30

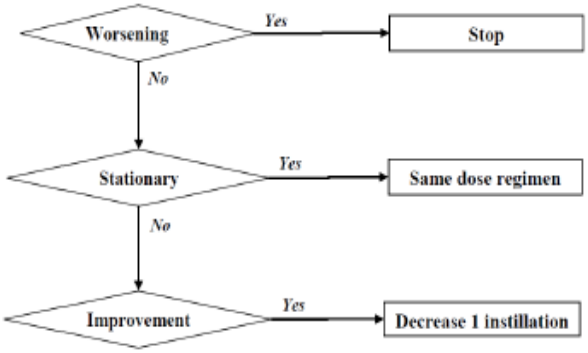


Figure 2 - Dose regimen algorithm at Day 90

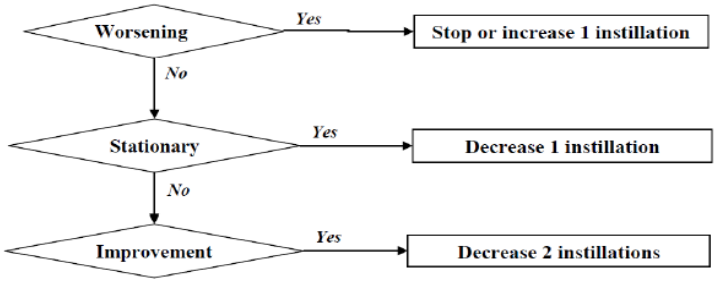
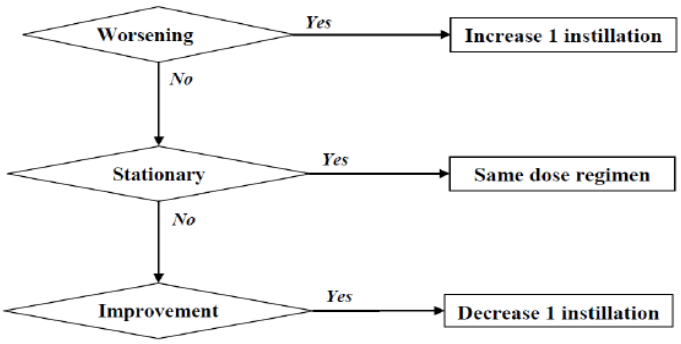


Figure 3 - Dose regimen algorithm from Day 180 to Month 48



Study Flow Chart

Table 1– Study flow chart

Visits Study window (days)	V1 (D -30)	V2 (D1)	V3 (D7)	V4 (D15)	V5 (D30)	V6 (D90)	V7 (D180)	V8 (M9)	V9 (M12)	V10 (M18)	V11 (M24)	V12 (M30)	V13 (M36)	V14 (M42)	V15 (M48)	V16 (M60)
SELECTION																
Selection criteria assessment	x															
Informed consent(1)	x						x			x			x		x	
COMPLIANCE																
Vials weigh-in(2)			(x)	(x)	x	x	x	x	x	x	x	x	x	x	x	x
Diary card(3)		x	(x)	(x)	x	x	x	x	x	x	x	x	x	x	x	x
EFFICACY																
Clinical evaluation		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmic evaluation (imaging)	x	x			x	x	x	x	x	x	x	x	x	x	x	x
SAFETY																
Physical examination and adverse events recording(4)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory parameters	x	x			x	x	x	x	x	x	x	x	x	x	x	x
Ocular pre-defined findings	x	x			x	x	x	x	x	x	x	x	x	x	x	x
DRUGS																
Concomitant therapies	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug dispensation		x			x	x	x	x	x	x	x	x	x	x	x	
Adaptive dose regimen					x	x	x	x	x	x	x	x	x	x	x	

(x) assessments if not a phone call visit
(1) Treatment dispensation was performed at the ophthalmology core laboratory after ophthalmologic examination and clinical assessment. Consequently, it was decided that the informed consent process for each extension would be conducted at the ophthalmology site.
(2) Vial weigh-in was intended to provide information on treatment compliance; not used due to inconclusive results
(3) Simplified version used from Month 30 to Month 60
(4) Adverse events collected from Day-30 up to 30 days after last study drug instillation

List of Investigators

Site	Status
Site 1	
Patrick Niaudet, Nephrologist	Coordinating Investigator and Principal Investigator
Dr Marina Charbit Nephrologist	Sub-Investigator
Dr Geneviève Guest, Nephrologist	Sub-Investigator
Site 2	
Dr. Chantal Loirat, Nephrologist (Up to January 2010)	Principal Investigator
Dr. Georges Deschenes, Nephrologist	Principal Investigator
Central Ophthalmology Center	
Dr. Christophe Baudouin	Physician responsible for ophthalmology evaluations
Dr. Antoine Labbe	Physician responsible for ophthalmology evaluations
Dr. Hong Liang	Physician responsible for ophthalmology evaluations

Study Endpoints

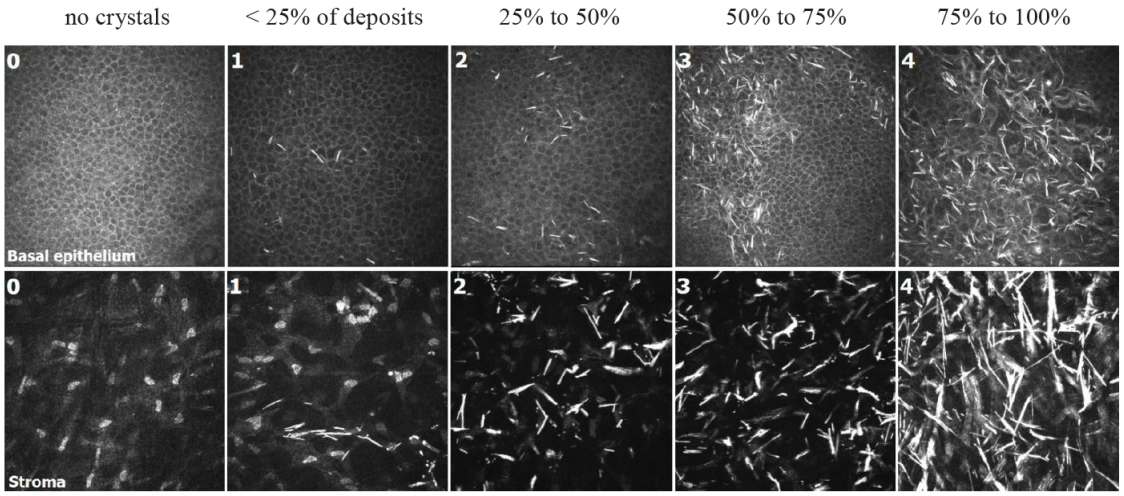
Primary Efficacy Endpoint

- Change in In Vivo Confocal Microscopy (IVCM) total score from baseline

Crystal density is rated on a scale of 0 to 4 in each corneal layer as:

0 = no crystals
1 = < 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

Figure 5 - In-Vivo Confocal Microscopy (IVCM) images (400 x 400 μm)



The IVCM total score was a composite of the IVCM score for each of the 7 corneal layers (2 layers in epithelium, Bowman's membrane, 3 layers in the stroma, and the endothelium); the presence of crystal deposits in each individual layer was graded on a scale from 0 to 4, so that the IVCM total score could range from 0 to 28. Higher total scores designate larger amounts of crystal deposits; a decrease in IVCM total score indicates a reduction in corneal crystals in at least one layer of the cornea.

IVCM images were obtained using the Rostock Cornea Module of the Heidelberg Retina Tomograph (HRT/RCM). At each site visit, 5-10 IVCM images of each layer were acquired in the central cornea of each eye by focusing the microscope from the superficial epithelial layer to the endothelium. IVCM images were evaluated and scored by the examiner.

Secondary Efficacy Endpoints

- Crystal thickness assessed by HRT-II
- Crystal thickness assessed by OCT
- Corneal cystine crystal score (CCCS) assessed by slit-lamp.
- Pain (100 mm Visual Analogue Scale [VAS]*)
- Photophobia (0-5 point scale)
- Visual acuity (logMAR scale)
- Visual contrast sensitivity

Statistical Analysis Plan

The primary efficacy criterion was the absolute change of the IVCM total score from baseline, assessed at each visit up to Month 60 of study treatment. As the IVCM score (individual and total) is measured for each eye, the reference unit for the analysis was the eye. The pairs of observations (the two eyes of a same person) are usually positively correlated. Statistical analysis of such cluster needs to take correlation into consideration; and a model-based analysis using a Generalized Estimating Equation (GEE) model was used. Working correlation matrices were defined. Inferential tests were applied to compare the absolute change from baseline (Day 1) for the IVCM total score, as response to Cystadrops treatment.

Descriptive statistics (value and absolute change from baseline Day 1) are presented for all secondary efficacy criteria and was analyzed at each visit, up to Month 60 of study treatment.

Two populations were defined in this study:

- Safety Set (SS): The SS included all patients/eyes who received at least one dose of CH 0.10% or Cystadrops
- Full Analysis Set (FAS): The FAS includes all patients/eyes who received at least one dose of Cystadrops and who have a baseline assessment and at least one ocular measurement post-dose.

An interim analysis of safety and efficacy parameters was performed after collection of data at Day 90. A second interim analysis was performed at Month 24; this analysis was the object of an interim study report dated March 2011. Annual interim statistical analyses were performed thereafter until Month 48.

6.1.2. Study CHOC

Study CHOC: "Cysteamine Hydrochloride for nephrOpathic Cystinosis, open-label Phase 3 pivotal study"

Primary Objective: To compare the efficacy of Cystadrops (cysteamine hydrochloride ophthalmic solution) 0.55% versus cysteamine hydrochloride 0.10% eye drops solution in terms of superiority in patients with nephropathic cystinosis.

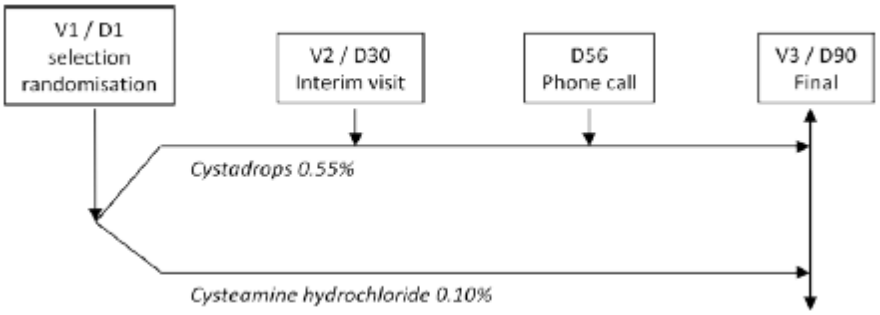
Secondary Objective: To evaluate the safety profile of Cystadrops in patients with nephropathic cystinosis.

Trial Design
This study was a 2 parallel-group, open-label, multi-center, randomized, comparative trial. At least 24 cystinosis patients of either sex and any age, with corneal cystine crystal deposits, treated by topical cysteamine with good compliance and able to comply with IVCM procedure were planned to be included in this study at 2 sites in France. In compliance with the recommendations of the EMA Protocol Assistance procedure, younger children for whom confocal microscopy may not be feasible could be included in the study but were not analyzed in the primary efficacy analysis. These patients were analyzed in the secondary efficacy analysis as well as the safety analysis. After enrollment, patients were randomized to receive one of the following eye drops for a 90 day period:

- Cysteamine hydrochloride 0.55% solution (Cystadrops)
- Cysteamine hydrochloride 0.10% solution

The eye drops were instilled as 1 drop per eye, 4 times per day when patient was awake: at approximately 8:00 am, 12:00 am, 4:00 pm and 8:00 pm. This was an open-label study; as the Cystadrops solution is more viscous than the control product, the study could not be conducted under blinded conditions.

Figure 1 - Treatment administration scheme



Inclusion Criteria

- Signed and dated written inform consent form in accordance with local regulations: Having freely given their written informed consent to participate in the study. For

patients aged less than 18 years consent will be obtained from the two parents (or legal representatives)
- Diagnosis of cystinosis based on a previous white blood cells cystine concentration >1.5 nmoles half-cystine per mg protein
- Presence of corneal crystal deposits attested by a slit-lamp examination within 3 months prior to inclusion
- Ability to comply with their usual eye drops treatment in order to comply with the eyewash regimen of 4 instillations
- Agreement to move to Ophthalmic Core Laboratory for the assessment visits,
- Likely to be able to participate in all scheduled evaluations and complete all required study procedures
- In the opinion of the investigator, the patient will be compliant and has a high probability of completing the study

Exclusion Criteria
- Patients with uncontrolled hepatic disorder, cardiovascular disease, neurologic disease, or cancer
- Patients with hypersensitivity to cysteamine, excipients (disodium edetate, benzalkonium chloride solution, carmellose Sodium ((b) (4)), citric acid monohydrate, sodium hydroxide)
- Laboratory tests out of normal range according to the reference laboratory values (deviations may be accepted if the investigator considers that they are not clinically significant for the conduct of study)
- Patients with history or presence of alcohol abuse or drug addiction
- Pregnant or breast-feeding women
- Women of child-bearing potential without effective contraception (oral pill or intra-uterine contraceptive device)
- Age less than 2 years and patients likely to be non-compliant to the study procedures or for whom a long-term follow-up seems to be difficult to achieve (In the younger children, the confocal microscopy may not be feasible and therefore will not be excluded from the study but only those patients able to undergo the IVCM procedure should be included in the primary analysis)

Treatments administered
Both study products were administered as follows: 1 eye drop in each eye 4 times a day (at approximately 8:00 am, 12:00 am, 4:00 pm and 8:00 pm) for 90 days. The investigational product, cysteamine hydrochloride 0.55% (Cystadrops), was provided in dark glass vial containing 5 ml of a viscous eye drops solution and was supplied by Orphan Europe.

The control product, cysteamine hydrochloride 0.10%, was obtained as a powder in vials and reconstituted at the time of use. This product was supplied by AGEPS, AP-HP Hospital Pharmacies at both sites. Study products were to be stored either at -20°C (Cystadrops) or at 2-8°C (cysteamine hydrochloride 0.10%), protected from light. After dispensing, they were to be

stored between 2 and 8°C. Vials stored according to the instructions could be used for 7 consecutive days.

Study Flow Chart

Table 1– Study flow chart

	D1	D30	D60*	D90
	Inclusion visit/V1	Interim visit/V2	Phone call	Final visit/V3
STUDY WINDOWS		+/- 4 days	*- 4days	+/- 4 days
SELECTION/ RANDOMIZATION				
Selection criteria assessment	X			
Informed consent	X			
Randomisation	X			
COMPLIANCE				
Diary card		X		X
Epithelial layers IVCM[a]	X	X		X
EFFICACY				
IVCM[a]	X	X		X
Photophobia	X	X		X
CCCS (by slit-lamp)	X	X		X
SAFETY				
Adverse events and Local Adverse Event Drug Reactions	X	X	X[c]	X
Ocular Exploration (visual acuity, ocular tonometry, eye fundus examination, fluorescein staining, refraction and corneal topography)	X	X		X
Health Outcome Assessment[d]	X	X		X
Laboratory: WBC cystine[b,]	X			X
DRUGS				
Concomitant therapies	X	X		X
Study drug dispensation	X	X	X	

a. In the younger children, the confocal microscopy may have not been feasible. Paediatric patients who did not undergo IVCM could be included, however, only patients able to undergo the IVCM procedure were included in the primary analysis. It was decided to assess compliance with treatment based solely on diary card data.
b .The latest available WBC cystine results were reported at inclusion visit (D1).
For final visit (D90) WBC cystine results, the latest available WBC results obtained during the course of the study were reported.
c. The data collected during the phone call was to be reported in the source document and transcribed on the appropriate eCRF page.
* Phone call at Day 56 to ensure subsequent dispensing of study product at D60.
d. Only performed in adult population (Cystadrops arm only)

List of Investigators

Site	Status	Number of Patients
Site 1		
Prof. Christophe Baudouin Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts (CHNO) Institut de la Vision 28 rue de Charenton 75012 Paris, France	Principal Investigator	28
Site 2		
Prof. Carole Burillon Groupement Hospitalier Edouard Herriot (HEH) Ophtalmologie - Pavillon C 5 place d'Arsonval 69003 Lyon, France	Principal Investigator	4

Study Endpoints

Primary efficacy endpoint

- Total score of the corneal cystine crystal density measured by In-Vivo Confocal Microscopy (IVCM) in the 7 corneal layers. Scores were assessed by an independent masked reader

Secondary Efficacy Endpoints:

- Photophobia (rated by investigator and patient)
- Corneal cystine crystal score (CCCS) by slit-lamp
- Crystal thickness measured by optical coherence tomography (OCT)

Safety Endpoints:

- Reported adverse events, local adverse drug reactions (LADRs) through patient diary (redness, blurring, itching, stinging and burning),
- Ophthalmic exam (visual acuity and contrast vision, refraction, ocular tonometry, corneal topography, fluorescein corneal staining)
- Laboratory assays (WBC cystine).

Statistical Plan
In this trial, the unit of randomization was the patient and the unit of analysis was the eye. Inferential tests were performed at the 5% level of significance. A generalized estimating equation (GEE) model was applied on the IVCM total score change at Day 90 from baseline with treatment arm as effect and IVCM total score at baseline as covariate. The structure of the variance-covariance matrix for the primary efficacy analysis was autoregressive. A parametric Analysis of Covariance (ANCOVA) was used to analyze the change at Day 90 from baseline for the secondary efficacy criteria, with the change from baseline as an outcome variable, treatment arm as effect and the value at baseline as covariate. The correlation between paired eyes was taken into account as repeated measurements within the subject in the model.

6.1.3. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs).

Financial Disclosure

See Financial Disclosure Template in Section 12.2. of this review.

Patient Disposition

Patient Disposition: Study OCT-1

Recruited in the Run-In Period (Day -30)	8
Continuation at Day 1	8
Competed at Day 180	8
Completed at Month 60	8
Study Discontinuation	0
Analysis Populations	
Safety Set	8
Full analysis Set	8

Patient Disposition: Study CHOC

Recruited in the Run-In Period (Day -30)	32
Completed at Month 3	31
Study Discontinuation	1
Analysis Populations	
Safety Set	32
Full analysis Set	32

Table of Demographic Characteristics

Demographics: Study OCT-1

Gender	
Male	2
Female	6
Age (years) At Time of Inclusion	
Mean (sd)	12.1 (4.6)
Min, Max	7, 21

Demographics: Study CHOC

Gender	Cystadrops N=15	CH 0.10% N=16
Male	7	8
Female	8	8
Age (years) At Time of Inclusion		
Mean (sd)	19.2 (15.5)	15.1 (10.3)
Min, Max	2.8, 62.6	3.5, 36.0

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study OCT-1
The mean (SD) duration of treatment with Cystadrops was 59.8 (0.21) months (range: 59.5 to 60.1 months.

Study OCT-1: Compliance (N=8)

	Instillations Prescribed-Mean	**Instillations Administered-Mean**
Day 1-30	4.0 (0.53)	4.0 (0.53)
Day 30-90	3.9 (0.83)	3.9 (0.83)
Day 90-180	2.9 (0.83)	3.0 (0.93)
Month 9-12	2.9 (0.83)	3.0 (0.93)
Month 12-18	2.9 (0.83)	3.0 (0.93)
Month 18-24	2.9 (0.83)	3.0 (0.93)
Month 24-30	2.8 (0.71)	2.9 (0.83)
Month 30-36	2.9 (0.83)	2.9 (0.83)
Month 36-42	2.9 (0.83)	2.9 (0.83)
Month 42-48	3.0 (1.07)	3.0 (1.07)
Month 48-60	3.0 (1.07)	3.0 (1.07)

Study CHOC: Treatment Exposure

	Cystadrops N=15	**CH 0.10% N=16**
Duration of Treatment (Days)		
Mean	86.3 (19.9)	92.7 (5.46)
Total Number of Instillations*		
Mean	316 (83.9)	370 (89.5)

*The theoretical duration of treatment was between 86 and 94 days, with a dose regimen of 4 drops per day for a theoretical total of 344 to 376 instillations.

Efficacy Results – Primary Endpoint

The IVCM total score was a composite of the IVCM score for each of the 7 corneal layers; the presence of crystal deposits in each individual layer was graded on a scale from 0 to 4, so that the IVCM total score could range from 0 to 28. Higher scores designate larger amounts of crystal deposits; a decrease in IVCM total score indicates a reduction in corneal crystals in at least one layer of the cornea.

Study OCT-1: Primary Efficacy Endpoint (IVCM Score)

	Day 1	**Day 30**	**Day 180**	**Month 12**	**Month 24**	**Month 36**	**Month 48**	**Month 60**
IVCM total Score								
N	16	16	16	16	16	16	16	16
Mean (sd)	11.38	9.88	8.63	8.13	7.88	7.50	8.19	7.94
Min, Max	7, 18	5,16	5, 18	5, 12	3, 15	3, 14	5, 15	3, 15
Change From Baseline								
Mean (sd)	0	-1.50 (2.45)	-2.75 (2.29)	-3.25 (2.08)	-3.50 (2.07)	-3.88 (2.31)	-3.19 (3.04)	-3.44 (2.78)
P Value		0.0381	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Change From Baseline (%)								
Mean (sd)	0	-11.73% (25.09%)	-25.76% (18.63%)	-30.16% (16.87%)	-33.12% (20.83%)	-35.78% (21.57%)	-29.58% (25.37%)	-32.71 (25.40%)

Reviewer's Comments:
The absolute mean change in IVCM total score from baseline was statistically significant at all time points.

Study CHOC: Primary Efficacy Endpoint at Month 3 (IVCM Score)

	Cystadrops N=22	**CH 0.10% N=20**	**P value**
IVCM Score at Baseline			
Mean	10.6 (4.2)	10.8 (3.5)	
Absolute Change From Baseline in IVCM Score			
Mean	-4.60 (3.1)	-0.455 (3.4)	<0.0001
Min, Max	-11.0, -0.600	-7.60, 6.50	
Percent Change From Baseline			
Mean	-40.4% (16.0)	-0.679% (33.0)	

Reviewer's Comments:
The absolute change from baseline in IVCM score compared between test drug and control was statistically significant at 3 months.

Cysteamine hydrochloride 0.10% eye drops is labeled to be given q2h while awake. In this trial it was only given qid; however, this was a superiority comparison not a noninferiority comparison, and it is acceptable that the product was not given as labeled.

Data Quality and Integrity
This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

Visual Acuity
Visual acuity was measured using the logMAR scale. A decrease in logMAR scale over time indicates an improvement in visual acuity. A 0.3 change is considered clinically significant.

Study OCT-1 Secondary Endpoint: Visual Acuity (LogMAR Scale)

	Day 1	**Day 30**	**Day 180**	**Month 12**	**Month 24**	**Month 36**	**Month 48**	**Month 60**
VA								
N	16	16	16	16	16	16	16	16
Mean (sd)	0.09 (0.13)	0.08 (0.07)	0.10 (0.12)	0.07 (0.12)	0.14 (0.10)	0.06 (0.11)	0.02 (0.10)	0.04 (0.10)

Study CHOC Secondary Endpoint: Change in Visual Acuity at Month 3 (LogMAR Scale)

	Cystadrops N=30	**CH 0.10% N=32**
Visit Day 30		
N	22	29
Mean (sd)	-0.056 (0.11)	-0.020 (0.09)
Visit Day 90		
N	22	29
Mean (sd)	-0.098 (0.015)	-0.069 (0.15)

Reviewer's Comments:
In both treatment arms, clinically insignificant improvement of visual acuity was observed over course of the study.

Photophobia
Photophobia was graded by the investigator at Day -30, Day 1 (baseline), Day 30, Day 90, Day 180, Month 9, Month 12, Month 18, Month 24, Month 30, Month 36, Month 42, Month 48, and Month 60. The investigator performed an objective assessment of photophobia during the examinations, grading photophobia on a scale from 0 (absence) to 5 (extreme).

Study OCT-1 Secondary Endpoint: Photophobia By Investigator

	Day 1	**Day 30**	**Day 180**	**Month 12**	**Month 24**	**Month 36**	**Month 48**	**Month 60**
Photophobia								
N	16	16	16	16	196	16	16	16
Mean (sd)	2.50	2.56	2.19	2.19	1.50	1.44	1.63	1.63

Study CHOC Secondary Endpoint: Photophobia By Investigator at Month 3

	Cystadrops N=30	**CH 0.10% N=32**	**P value**
Mean	-0.633 (0.77)	0.065 (0.44)	0.0048
Min, Max	-2.00, 0	-1.00, 1.00	

Dose/Dose Response
Not applicable.

Durability of Response
Cystadrops is intended to treat a chronic condition.

Persistence of Effect
Not applicable.

Additional Analyses Conducted on the Individual Trial
None.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary efficacy endpoint for studies OCT-1 and CHOC (change in mean IVCM score) achieved their primary endpoint.

7.1.2. Secondary and Other Endpoints

See Section 6.1.2.

7.1.3. Subpopulations

Both Studies OCT-1 and CHOC were too small in number to do any subpopulation assessment.

7.1.4. Dose and Dose-Response

Not applicable.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

See 6.11 and 6.22 of this review. Cysteine crystals constantly reform and deposit. Cystinosis The, requires life-long therapy with topical ophthalmic solution in conjunction with oral cysteamine tablets.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Post-market Setting

Per the Periodic Safety Update Report (PSUR) covering 19 July 2018 to 18 January 2019:

> An estimated total of 844 patients have been exposed to Cystadrops through the Named Patient Use (NPU) programs (393 patients in the EU [including 130 patients in France] and 451 patients in other countries including Iceland, Switzerland, Russia, Brazil, India, Argentina, Columbia, Norway, South Korea and Hong Kong, as well as those in the Middle-East and North Africa region). The overall benefit-risk profile of Cystadrops remains favorable when the drug is used in its approved indication and duration of

treatment, and in accordance with the appropriate contraindications, warnings and precautions included in the current prescribing information.

7.3. Integrated Assessment of Effectiveness

The data contained in this submission establishes the efficacy of Cystadrops ophthalmic solution dosed qid for the treatment of corneal cystine crystal deposits in adults and children with cystinosis

8. Review of Safety

8.1. Safety Review Approach

The main support for safety is from 2 clinical studies (Studies OCT-1 and CHOC) and the reference to Agency's finding of safety for NDA 20-392.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Study OCT-1 enrolled 8 patients and had a duration of 5 years. Study CHOC enrolled 32 patients and had a duration of 3 months. Reference to the Agency's findings for NDA 20-392 supports systemic safety at higher concentrations than can be achieved by ocular administration. See Section 6.1.2 for more details.

8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat. The safety population included only subjects with cystinosis.

8.2.3. Adequacy of the safety database:

Being an (b) (4), the safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

AEs were classified by MedDRA system organ class (SOC).

8.3.3. Routine Clinical Tests

See section 8.4.6.

8.4. Safety Results

8.4.1. Deaths

No deaths in either study.

8.4.2. Serious Adverse Events (SAE)

Study OCT-1
Six patients experienced a total of 48 SAEs; of these, 46 were hospitalizations related to the underlying cystinosis disease and not to the topical administration of Cystadrops. Of the 2 remaining SAEs, 1 (corneal neovascularization) was reported as medically significant and 1 (knee deformity) was reported as persistent or significant disability/incapacity.

Narrative of Patient with SAE of corneal neovascularization:
This (b) (6) with nephropathic cystinosis was diagnosed in (b) (6), when the patient was (b) (6). The patient underwent a kidney transplant in (b) (6). On (b) (6), the patient started treatment with Cystadrops at 1 drop/eye, 4 times a day. On (b) (6) presented a moderate increase in corneal neovascularization in both eyes. Starting from the day of the event, the patient received symptomatic treatment with Vexol (rimexolone) at a daily dose of 2 drops/eye. Treatment with Cystadrops was continued, and the daily dose was increased to 5 drops/eye. The patient was reported as not recovered from the event. The investigator initially reported the relationship of this event to treatment as "unknown." According to the Investigator Brochure (Version 3, dated 08 October 2012), the increase in corneal neovascularization is unexpected. Based on the available information, the investigator and the sponsor considered that there was a "reasonably possible" causal relationship between Cystadrops and the increase in corneal neovascularization. This patient also experienced other events which were reported as serious: papilledema ((b) (6)), lumbar puncture followed by vomiting/post-lumbar puncture syndrome ((b) (6)), blood creatinine increased/transplant rejection ((b) (6)), immunoglobulin therapy/allergy to immunoglobulin therapy ((b) (6)), gastroenteritis/acute renal failure ((b) (6)), and artero-venous fistula operation ((b) (6)).

Study CHOC: Serious AEs

Patient	Description
Patient (b) (6)	This (b) (6) was included in the study and randomized to the Cystadrops arm on (b) (6) had a history of otitis in (b) (6). Nephropathic cystinosis was

	diagnosed in (b) (6). At the time of the event, the child was treated for cystinosis with RP103 (cysteamine bitartrate) 800 mg/day, sodium bicarbonate 9 g/day, INDOCID (indomethacin) 42 mg/day, PHOSPHONEUROS (phosphoric acid, magnesium, calcium) 120 drops/day, LEVOCARNYL (levocarnitine) 10 ml/day and had 2 patches/month of EMLA (prilocain, lidocain) for blood sampling pain prophylaxis. On (b) (6), 39 days after treatment initiation, the patient suffered from gastroenteritis of moderate intensity, for which (b) (6) was admitted to emergency ward during 6 hours. The patient received TIORFAN (racecadotril) 60 mg/day, DOLIPRANE (paracetamol) syrup 4 dose/weight daily and GES45 (oral glucose and saccharose, sodium and potassium), as needed, from (b) (6). The event abated on (b) (6); the study treatment was not discontinued for this event and the patient completed the trial on (b) (6). The investigator considered the event as medically significant to be declared as a serious adverse event.
Patient (b) (6)	This (b) (6) was included in the study and randomized to the Cystadrops arm on (b) (6). Nephropathic cystinosis was diagnosed in (b) (6); the patient had kidney transplantation in (b) (6), and presented with neovascularization of the left cornea and corneal inflammation at baseline (b) (6). The patient has a history of controlled melanoma of the left ankle since (b) (6), and basocellular carcinoma of the right nostril operated in (b) (6). At the time of the event, the patient was treated with CYSTAGON (cysteamine bitartrate) 2400 mg/day for cystinosis, INDOCOLLYRE (indomethacin) eye drops for corneal inflammation, and mycophenolate mofetyl 1500 mg/day and NEORAL (cyclosporin) 3 mg/day for kidney transplantation. On (b) (6), 8 days after treatment initiation, the patient suffered from moderate tiredness due to cystinosis for which (b) (6) was hospitalized from (b) (6) to (b) (6) to have a rest, without the addition of any other treatment. The event abated on (b) (6). The study treatment was not discontinued for this event and the patient completed the trial on (b) (6).
Patient (b) (6)	This (b) (6) was included in the study and randomized to cysteamine hydrochloride 0.10% arm on (b) (6) has no reported medical history besides nephropathic cystinosis, diagnosed in (b) (6). At the time of the event, the child was treated for cystinosis with CYSTAGON (cysteamine bitartrate) 600 mg/day, sodium bicarbonate 1500 mg/day, sodium chloride 750 mg daily, PHOSPHONEUROS (phosphoric acid, calcium phosphate, magnesium) 20 drops/day, INDOPAED® (indomethacin) 2 mL/day, and FERROSTRANE (sodium feredetate) 2 teaspoons/day since (b) (6) also received MOPRAL (omeprazole) 10 mg daily as needed from (b) (6) to (b) (6) for prevention of vomiting. On (b) (6), 52 days after treatment initiation, the patient suffered from gastroenteritis of mild intensity with vomiting and dehydration, for which (b) (6) was hospitalized from (b) (6). The patient received sodium and potassium perfusion intravenously, as needed, as treatment for dehydration. No laboratory test was performed. The study treatment was not discontinued for this event and the patient completed the trial on (b) (6).

Patient (b) (6)	This (b) (6) was included in the study and randomized to cysteamine hydrochloride 0.10% arm on (b) (6). Nephropathic cystinosis was diagnosed in (b) (6). The patient had renal failure due to cystinosis since (b) (6) with renal transplantation in (b) (6) and its rejection in (b) (6), and a left corneal transplant on (b) (6). Other relevant history included HTN since (b) (6), DM since (b) (6), acute pancreatitis due to a CFTR gene heterozygote mutation in (b) (6), arteriovenous fistula of the left arm, and breast fibroma at an unspecified time. At the time of the event, the patient was treated for cystinosis with CALCIDIA (calcium) 3080 mg/day, SPECIAFOLDINE (folic acid) 5 mg/day, UN-ALFA (alfacalcidol) 0.25µg/day, UVEDOSE (cholecalciferol) 100 000 IU/month, DACUDOSE (sodium borate) 3 doses/day, CELLUVISC (carmellose sodium) 6 drops/day, retinol ophthalmic cream as needed. For (b) (6) corneal transplantation, the patient was treated with cyclosporin 2% 2 drops/day since (b) (6), Tobradex qid since (b) (6). Renal failure treatments included dialysis 3/week with EMLA patch (prilocain-lidocaine) for pain prophylaxis before dialysis, RENAGEL (sevelamer) 6400 mg/day, sodium 1 spoon/day without dialysis and MIMPARA (cinacalcet) 90 mg/day. Other treatments included AMLOR (amlodipine) 10 mg/day and atenolol 25 mg/day for arterial hypertension, and GLUCOPHAGE (metformin) unknown dose for diabetes. From (b) (6), the patient experienced non-serious moderate blurred vision, itching and burning of both eyes, lasting more than 1 hour, considered possibly related to study treatment by both the investigator and the sponsor. (It should be noted that the patient used, on average, more than 4 drops of cysteamine hydrochloride per day during the treatment period). On (b) (6), 7 days after treatment initiation and 18 days after the surgery, the patient was hospitalized for rejection of corneal grafting of (b) (6) left eye, with superficial keratitis, and chemosis with photophobia. The study treatment was temporarily interrupted for both eyes from (b) (6) and re-started the treatment on right eye only on (b) (6). The event abated after corrective treatment, the patient was discharged on (b) (6) and completed the trial on (b) (6).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study OCT-1: None of the patients discontinued treatment (either permanently or temporarily) due to an AE.

Study CHOC: Two patients (1 in each treatment arm) temporarily discontinued treatment due to AEs; 1 additional patient in the Cystadrops arm discontinued at Day 86 due to allergic conjunctivitis and did not restart treatment.

8.4.4. Significant Adverse Events

See Section 8.4.2.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study OCT-1: Treatment Emergent Adverse Events

System Organ Class	Number of Events
Eye disorders	5
Infections and infections	8
Surgical and medical procedures	12
Musculoskeletal disorders	7
Nervous system disorders	8
Renal and urinary disorders	2
GI disorders	3
Immune system disorders	4
Injury, poisoning, and procedural complications	4
Investigations	5
Metabolism disorders	7
Ear disorders	1
Reproductive disorders	1
Skin disorders	1
Social circumstances	1
Blood disorders	2

Study OCT-1: Ocular Treatment Emergent Adverse Events

	Number of Events
Chalazion	1
Corneal neovascularization	0
Dry eye	0
Hordeolum	1
Papilledema	1

Study CHOC: Treatment Emergent Adverse Events

System Organ Class	Number of Events Cystadrops N=15	Number of Events CH 0.10% N=16
Eye disorders	31	57
Infections and infections	7	6
Respiratory disorders	1	2
Nervous system disorders	3	0
General disorders	2	0
Injury, poisoning, and procedural complications	1	1
Metabolism disorders	1	1
Musculoskeletal disorders	2	0
Investigations	2	0
Ear disorders	1	0
GI disorders	1	0
Immune system disorders	1	0
Renal disorders	1	0
Skin disorders	0	1
Social circumstances	1	
Vascular disorders	0	1

8.4.6. Laboratory Findings

Study OCT-1: Chem 7, CBC, and Urinalysis was collected in this study. Clinically significant out-of-range values were reported for 3 patients: elevated creatinine for 2 patients (Patient No. (b) (6) at Month 12, and Patient No. (b) (6) at Month 36 and Month 42) and hypokalemia for 1 patient (Patient No. (b) (6) at Month 48).

Study CHOC: Concentration of cystine in WBC on Day 90 and at baseline. As expected, patients for whom cystine was measured showed levels above the normal range of < 0.2 nmol/mg protein at both time points. There appeared to be no clinically relevant change in the levels of cystine.

8.4.7. Vital Signs

Vital signs were not monitored.

8.4.8. Electrocardiograms (ECGs)

Not performed.

8.4.9. QT

Not applicable.

8.4.10. Immunogenicity

Not applicable.

8.4.11. Human Reproduction and Pregnancy

This drug has not been tested in pregnant women.

8.4.12. Pediatrics and Assessment of Effects on Growth

Height and growth were not monitored in these trials.

There is an agreed PSP under IND 140943 requesting - a deferral to conduct study post approval for 0 months to 2-year-old children. The Pediatric Review Committee discussed the application on 12/17/2019.

Timeline:

- Estimated protocol submission date: No later than February 4, 2019
- Estimated study initiation date: No later than March 31, 2019
- Estimated study completion date: No later than December 31, 2021
- Estimated final report submission date: No later than June 30, 2022

8.4.13. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Cystadrops is a non-narcotic and does not have abuse potential.

8.5. Safety in the Post-market Setting

8.5.1. Safety Concerns Identified Through Post-market Experience

None.

8.5.2. Expectations on Safety in the Post-market Setting

Per the Periodic Safety Update Report (PSUR) covering 19 July 2018 to 18 January 2019:

No safety signals were newly identified, ongoing or closed during the reporting period. A summary of the safety concerns for Cystadrops at the beginning of the reporting period for this PSUR is presented in Table 8.

Table 8: Summary of safety concerns

Important identified risks	• Severe eye irritation
Important potential risks	• Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) • Corneal neovascularisation • Ocular manifestations of Ehlers-Danlos like syndrome (EDLS) • Increased risk of infection and medication error due to device assembly failure
Missing information	• Patients with other ocular co-morbidities • Patients receiving concomitant treatment with ophthalmic products containing BAK • Long-term safety

BAK=Benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome.
Source: Cystadrops Risk Management Plan (RMP) Version 1.3 (dated 30 September 2015), Module SVIII, Table 14.

8.5.3. Additional Safety Issues From Other Disciplines

None.

8.6. Integrated Assessment of Safety

The data contained in this submission establishes the safety of Cystadrops ophthalmic solution dosed qid for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.

9. Advisory Committee Meeting and Other External Consultation

There were no issues identified in the review of the application that were thought to benefit from an Advisory Committee discussion.

10. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

11. Postmarketing Requirements and Commitments

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

12. Financial Disclosure

Covered Clinical Study (Name and/or Number): OCT-1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 8		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator in Sponsor: Not applicable		

Covered Clinical Study (Name and/or Number): CHOC

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator in Sponsor: Not applicable

13. Labeling Recommendations

Labeling recommendations are provided in track changes in the draft revised package insert attached to the end of this review. Carton and Container labeling and Instruction for Use labeling are not attached.

This labeling is DRAFT and is not meant for transmission to the applicant. Not all disciplines were able to finalize their labeling comments this review cycle because of application deficiencies.

The Division will continue to work with the applicant on labeling.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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01/22/2020 07:43:38 AM

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