CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial #:	211302
Drug Name:	Cystadrops® (cysteamine ophthalmic solution) 0.37%
Indication(s):	Treatment of corneal cystine crystal deposits in adults and children with cystinosis
Applicant:	Recordati Rare Diseases Inc.
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Statistical Reviewer:	Solomon Chefo, Ph.D.
Concurring Reviewers:	Yan Wang, Ph.D., Team Leader
Medical Division:	Division of Transplant and Ophthalmology Products (DTOP)
Clinical Team:	Sonal Wadhwa, MD, Medical Officer William Boyd, MD, Team Leader
Project Manager:	Lois Almoza

Keywords: Cystinosis**,** In Vivo Confocal Microscopy (IVCM), corneal cystine crystal score (CCCS), GEE Model

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1 EXECUTIVE SUMMARY

In this New Drug Application (NDA), the applicant seeks approval of Cystadrops® 0.37% (hereafter referred to as Cystadrops) for the treatment of corneal cystine crystal deposits in adults and children with cystinosis (a rare genetic disorder). Corneal cystine crystals are an ocular manifestation of cystinosis resulting in photophobia (light sensitivity), ocular discomfort, blurred vision, and recurrent epithelial erosions if left untreated.

The test product, Cystadrops (a topical cysteamine hydrochloride ophthalmic solution dosed one drop in each eye, four times a day during waking hours), was first approved for the treatment of corneal cystine crystal deposits by the European Commission in January 2017 and in Canada on February 2019. Currently, Cystadrops is licensed in 31 countries worldwide. The initial approval of Cystadrops was based on the safety and efficacy findings in a pilot Phase 1/2a study (OCT-1) and a pivotal Phase 3 study (CHOC) both conducted in France.

This NDA is based on the efficacy and safety findings from the CHOC and OCT-1 studies supplemented by data from nine published studies on other ocular formulations containing the active substance, cysteamine hydrochloride.

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.

The mean change in the total IVCM score at Day 90 was the primary efficacy variable in the CHOC study. The mean change in CCCS, photophobia, and CT at Day 90 were secondary efficacy variables. In OCT-1 study, the mean change in the IVCM total score from baseline at each visit through Month 60 was the primary efficacy variable; the change in CCCS, photophobia, and CT were assessed over time as supporting analysis.

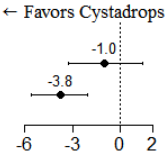
In the CHOC study, Cystadrops treated eyes demonstrated substantial reduction in the mean change in the total IVCM score from baseline during the study compared to CH 0.10% treated eyes (See Table 1 below). For example, at Day 90, Cystadrops and CH 0.10% treated eyes, respectively, had an average reduction of 4.6 units and 0.5 units in the total IVCM score from baseline. The treatment difference (*Cystadrops minus CH 0.10%*) in the mean reduction in the total IVCM score at Day 90 was 3.8 (95% confidence interval: (2.1, 5.6); p-value < 0.001).

Cystadrops treated eyes also demonstrated significant reduction in the secondary efficacy variables of CCCS, photophobia, and CT compared to CH 0.10% treated eyes. For example, at Day 90, Cystadrops treated eyes yielded about a 0.6-unit reduction in CCCS and in photophobia, and a 46 µm reduction in CT from baseline whereas CH 0.10% treated eyes showed worsening in these variables (See Table 1). Additionally, as shown in Figure 5 and Figure 10, 30% and 47% of Cystadrops treated eyes demonstrated at least 1-unit improvement in CCCS and in photophobia, respectively, from baseline compared to 0% and 6% of CH 0.10% treated eyes.

Table 1: Summary of mean change in IVCM, CCCS, Photophobia, and CT over time (Full Analysis Set [a])

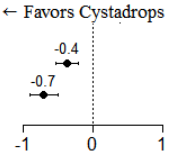
IVCM

Visit	Cystadrops (N = 20)	CH 0.10% (N = 20)	Difference (95% CI)
Baseline	10.6 (4.18)	10.8 (3.47)	
Day 30	-1.95 (2.70)	-0.44 (3.00)	-1.0 (-3.3, 1.4)
Day 90	-4.60 (3.12)	-0.45 (3.38)	-3.8 (-5.6, -2.1)



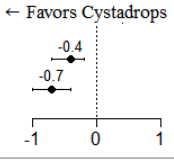
CCCS

Visit	Cystadrops (N = 30)	CH 0.10% (N = 31)	Difference (95% CI)
Baseline	2.26 (0.56)	1.98 (0.50)	
Day 30	-0.38 (0.39)	0.02 (0.22)	-0.4 (-0.5, -0.2)
Day 90	-0.59 (0.52)	0.10 (0.24)	-0.7 (-0.9, -0.5)



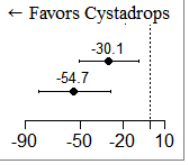
Photophobia

Visit	Cystadrops (N = 30)	CH 0.10% (N = 31)	Difference (95% CI)
Baseline	1.87 (1.17)	1.68 (1.05)	
Day 30	-0.33 (0.48)	0.10 (0.47)	-0.4 (-0.7, -0.2)
Day 90	-0.63 (0.76)	0.06 (0.44)	-0.7 (-1.0, -0.4)



CT

Visit	Cystadrops (N = 30)	CH 0.10% (N = 31)	Difference (95% CI)
Baseline	275 (159)	260 (167)	
Day 30	-21.7 (48.00)	8.52 (30.97)	-30.1 (-51.4, -8.7)
Day 90	-46.3 (55.33)	10.59 (43.55)	-54.7 (-80.4, -28.9)



[a] Included all randomized subjects who received at least one dose of study medication and who had a baseline assessment and at least one post-baseline assessment. Note that 10 eyes in the Cystadrops group and 11 eyes in the CH 0.10% group who had no baseline total ICVM data were excluded in the IVCM analysis.

The treatment benefit of Cystadrops in improving IVCM, CCCS, CT, and photophobia was also seen in the single arm OCT-1 study. In this study, Cystadrops treated eyes yielded a reduction in IVCM (Figure 3), CCCS (Figure 6), CT (Figure 8), and photophobia (Figure 11) from baseline over time. Also, most of the published literatures provided supportive evidence regarding the treatment benefit of Cystadrops in improving corneal crystals density and photophobia.

In summary, based on the totality of evidence from the CHOC and OCT-1 studies and supporting data from the published literatures, the reviewer concludes that the application provided substantial evidence of efficacy of Cystadrops for the reduction of corneal cystine crystal density as measured by IVCM and using corneal cystine crystal score.

2 INTRODUCTION

2.1 Overview

In this NDA submission, the applicant seeks approval of Cystadrops in the United States (US) for the treatment of cystine crystal deposits in adults and children with cystinosis.

Cysteamine ophthalmic solution is currently indicated to reduce corneal cystine crystal deposition and there are two different commercial topical preparations of cysteamine currently available in the market:

- **Cystaran®**, a topical cysteamine hydrochloride ophthalmic solution administered one drop every waking hour, approved by the U.S. FDA in October 2012 (NDA 200740). Cystaran® is a non-viscous formulation.
- **Cystadrops®**, a topical cysteamine hydrochloride ophthalmic solution dosed one drop in each eye four times a day during waking hours (4 hours between each instillation), approved by the European Commission in January 2017 and in Canada on February 2019. Cystadrops® is a viscous formulation.

Cystadrops is currently licensed in 31 countries worldwide. The initial approval of Cystadrops was based on the safety and efficacy findings in **a Phase 1/2a and a Phase 3** studies (See Table below for a summary of these studies) both conducted in France.

Table 12 Overview of the Clinical Studies

Study ID (Country)	Study Design and Objectives	Population	Treatment schedule/duration	Study groups	Number of patients (eyes)		
					Safety Set	Full Analysis Set	Per-protocol Set
OCT-1 study (France)	Open-label, single-group Phase I/IIa trial. Initially planned for a period of 6 months; extended to 5 years. Primary objective: safety of Cystadrops (LADRs, AEs and SAEs; ocular parameters) Secondary objectives: 1) identification of lowest effective dose and 2) efficacy of Cystadrops (primary endpoint = change in IVCM score)	Male and female cystinosis patients, ≥ 3 yrs of age, with corneal cystine crystal deposits. Total enrolled: 8 patients Mean (± SD) age at inclusion: 12.1 (± 4.6) yrs; 4 patients <12 yrs, 3 patients 12 to < 18 yrs, 1 patient ≥ 18 yrs 2 (25%) of the patients were male.	Run-in period: usual treatment with CH 0.10% (allowed: 3 – 6 instillations/eye per day). Treatment period: treatment with Cystadrops was initiated at the same dosing frequency Dose adaptation up to Month 48. Treatment extended up to 5 years (60 months).	Cystadrops	8 (16)	8 (16)	not defined
CHOC study (France)	Open-label, randomized, comparative Phase III trial lasting for 3 months. The study had 2 parallel treatment arms: Cystadrops and CH 0.10%. Primary objective: superiority of Cystadrops *versus* CH 0.10% for efficacy (primary endpoint = change in IVCM total score). Secondary objective: safety of Cystadrops (LADRs, AEs and SAEs; ocular parameters)	Male and female cystinosis patients, ≥ 2 years of age, with corneal cystine crystal deposits. Total enrolled: 32 patients (1 adult patient lost to follow-up) Mean age (± SD) at inclusion: 17.1 (± 13.0) years; 13 patients <12 yrs, 6 patients 12 to < 18 yrs, 12 patients ≥ 18 yrs. 15 (48.4%) of the patients were male.	4 instillations/eye/day for a period of 90 days	Total Cystadrops *(with IVCM at baseline)* CH 0.10% *(with IVCM at baseline)*	31 (62) 15 (30) 16 (32)	31 (62) 15 (30) *11 (22)* 16 (32) *11 (20)*	23 (46) 12 (24) *9 (18)* 11 (22) *8 (15)*

AE = adverse event; CH = cysteamine hydrochloride; EU = European Union; ID = identification; IVCM = *in-vivo* confocal microscopy; LADR = local adverse drug reactions; SAE = serious adverse event; SD = standard deviation

This NDA is based on the efficacy and safety findings from the CHOC and OCT-1 studies supplemented by data from nine published studies on other ocular formulations containing the active substance, cysteamine hydrochloride.

The development plan of Cystadrops for the indication sought was scheduled to be discussed with the Agency on May 15, 2018 in a Pre-NDA meeting, but the meeting was cancelled after the applicant received the Agency's feedback. As part of the meeting package, the applicant sought the Agency's feedback if the clinical data in the two studies (including supporting safety data from the Named Patient Use (NPU) programs) are enough in supporting Cystadrops for the indication sought. Based on review of the Pre-NDA document, the Agency responded that "*full study reports of the two studies need to be submitted before the acceptability of the endpoint can be established*". Of note, the primary endpoint in both studies was the change from baseline in the total IVCM score at Day 90 in the CHOC study and at each time-point in the OCT-1 study. After receipt of the NDA submission, the Agency confirmed the acceptability of the endpoint for the indication sought.

Regarding the applicability of the submission solely relying on foreign data, the medical review team confirmed the applicability of the France patient population to the US population.

2.2 Data Sources

The primary data source for this review were the clinical study reports and the analyses and tabulation datasets of Study OCT-1 and CHOC. These were provided in an electronic submission and are located at \\CDSESUB1\evsprod\NDA211302\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\nephropathic-cystinotic-patients-with-corneal-cystine-crystal-de\. The primary analysis datasets are located at \\CDSESUB1\evsprod\NDA211302\0003\m5\datasets\.

The NDA also included summary of nine published literatures in Section 2.7.3.4 of the CHOC Clinical Summary Document (Module 2.7).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer found the quality of the submitted data and analysis acceptable.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study Design

The main efficacy support for Cystadrops in the reduction of corneal cystine crystal deposits was primarily based on two clinical studies: a pivotal Phase 3 study (CHOC) and a supportive Phase 1/2a study (OCT-1) both conducted in France.

CHOC was a 3-month, open-label, randomized, multi-center, active-controlled Phase 3 study designed to demonstrate the superiority of Cystadrops to the standard of care in France (CH 0.10%) in reducing corneal cystine crystal deposits. This study was conducted at 2 sites in France. The study was initiated on 09 January 2013 and completed on 28 June 2013.

In the CHOC 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% and 31subjects (62 eyes) received at least one dose of study drug. The total treatment duration was 90 days and subjects were to receive one eye drop of the treatment regimen in each eye 4 times a day at approximately 8am, 12am, 4pm and 8pm. During the treatment period, subjects had scheduled visits on Day 1, Day 30, Day 60 (Phone call), and Day 90.

Study OCT-1 was an open-label, adaptive, dose-response Phase 1/2a study designed to establish the safety, lowest effective dose regimen, and efficacy of Cystadrops. This study was conducted at 2 sites in France. The study was initiated on 12 February 2008 and completed on 23 April 2013. In this study, a total of 8 subjects (16 eyes) at least 3 years of age with corneal cystine crystal deposits were enrolled to receive study treatment in both eyes for five years. The study was initially planned for six months but was later extended for five years. In this study, subjects underwent a 1-month run-in period followed by a treatment period: subjects received 3-5 instillation per eye per day of CH 0.10% during the run-in period and Cystadrops with the same dosing frequency during the treatment period.

During the treatment period of the OCT-1 study, dose regimen was adapted according to ocular findings at Day 30, Day 90, Day 180, Month 9, Month 12 and subsequently every 6 months until Month 48. Per the study report, 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). In this study, on the average, Cystadrops was instilled 3 times per day from Month 1 onward.

Efficacy Evaluation

The primary efficacy evaluation in both studies was based on the corneal cystine crystal density as measured by IVCM in both eyes. Per the study protocols, the IVCM images in the CHOC study were evaluated and scored by a single and independent masked reader whereas in the OCT-1 study none of the evaluations were performed in a masked manner.

According to the submission, IVCM is the most recent and the most precise measurement based on anterior segment optical tomography. IVCM provides a quantitative evaluation of the cystine crystals in seven layers of the cornea through multiple images (i.e. two layers in the **epithelium** [epithelium and basal epithelium], **Bowman's membrane**, three layers in the **stroma** [superficial, medium, and deep stroma], and the **endothelium**). Each layer was scored in 0-4 scale: 0 = no crystals, 1 = < 25% of deposits in the images, 2 = 25% - 50% of deposits in the images, 3 = 50% - 75% of deposits in the images, and 4 = 75% - 100% of deposits in the images.

In both studies, additional efficacy evaluation was done based on: (i) **crystal thickness** (as assessed by optical coherence tomography (OCT) and Heidelberg Retina Tomograph [HRT-II] in the OCT-1 study, (ii) density of corneal cystine crystals as assessed during slit lamp examination using **corneal cystine crystal score (CCCS)**, and (iii) **photophobia** (as assessed by the investigator during slit-lamp examination) considered as one of the clinical symptoms of cystinosis.

- CCCS was scored in a 0 to 3 scale in 0.25 increments: 0.00 (clarity at the center) to 3:00 (greatest recognizable crystal density).
- Photophobia was assessed on a 0 to 5 scale based on an objective assessment by the investigator: 0 (absence) to 5 (extreme). In the CHOC study, patients also rated signs and symptoms of photophobia on a 0 to 5 scale: 0 (no difficulty experienced) to 5 (extreme photophobia causing the patient to stay indoors, cannot stand the natural light even with dark glasses).

Primary Efficacy Endpoint

The primary efficacy endpoint in the pivotal CHOC study was **the change in the total IVCM score from baseline at Day 90**. The total IVCM score was a composite score of the scores attributed to the seven layers of the cornea (range: 0-28). The change in the total IVCM score from baseline at each visit through Month 60 was the primary efficacy variable in the OCT-1 study. The change in CCCS, CT, and photophobia at Day 90 in the CHOC study and at each visit in the OCT-1 study were assessed as supporting analyses. In CHOC study, the primary efficacy variable was analyzed by the subgroup of age (children [< 18 years] versus adults [≥ 18 years]) as an exploratory analysis.

3.2.2 Statistical Methodology

Primary Efficacy Analysis

The applicant's primary efficacy analysis in the pivotal CHOC study evaluated superiority of Cystadrops to CH 0.01% in the mean change in the total IVCM score from baseline at Day 90 using a generalized estimating equation (GEE) model. The GEE model included treatment as a factor and baseline IVCM score as a covariate. Since both eyes of a subject were included in the study, the

applicant used an autoregressive (AR [1]) covariance-structure to account for the correlation between eyes of the same subject. Based on the GEE model, p-values and two-sided 95% CIs for the treatment difference (*Cystadrops minus CH 0.01%*) in the mean change in the total IVCM score from baseline at Day 90 were provided to determine superiority.

In the OCT-1 study, the primary efficacy variable of the mean change in IVCM from baseline at each visit was summarized for Cystadrops using descriptive statistics. In this study, the secondary efficacy variables were also summarized using descriptive statistics.

The primary efficacy analysis in both studies was based on the full analysis set (FAS) including all randomized subjects who received at least one dose of study medication and had a baseline assessment and at least one post-baseline assessment. As a sensitivity analysis, the primary efficacy analysis was also performed on the per-protocol population which included all subject in the FAS population without a major protocol violation.

To compare the treatment groups in the secondary efficacy variables of the mean change in CCCS, CT, and photophobia, the applicant used analysis of covariance model (ANCOVA) using treatment and the corresponding baseline values as a covariate. The applicant used unstructured covariance-structure to account for the correlation between eyes of the same subject. As shown in Figure 13, a strong correlation existed between measurements of the two eyes in these variables at each study visit. Based on the model, p-values were reported for descriptive use in the study report.

Reviewer's Remark:

i) Due to the small sample size of the study, as a supporting/sensitivity analysis, the reviewer analyzed the primary efficacy variable using ANCOVA model based on bootstrap samples to assess the robustness of the results from the GEE model.

In the bootstrap approach, 500 bootstrap samples were selected with replacement from the original data. In each bootstrap sample, the number of subjects per treatment group and the number of young children per treatment group were set fixed as in the original sample. Based on the treatment differences in the 500 bootstrap samples, 95% confidence interval for the treatment difference was derived by computing the 2.5% and 97.5% percentiles of the treatment differences in the bootstrap samples. P-value to test the treatment difference based on the bootstrap samples was calculated using 500 permutation samples. As shown in Section 3.2.4, except for minor numerical differences, the bootstrap approach yielded comparable results to the GEE model. Similar analyses were performed to evaluate the secondary efficacy variables.

ii) Additional sensitivity analysis was also performed for the IVCM endpoint in the CHOC study by taking the average of the two eyes. As shown in Appendix Table 11, analysis based on the average of two eyes also yielded comparable results to the GEE model.

iii) In the primary efficacy analysis, the applicant used AR [1] covariance-structure to account for the correlation between eyes of the same subject. It should be noted that since the correlation between two eyes requires a single parameter, any covariance-structure could be used in the model. Also, the applicant used GEE model for the analysis of primary efficacy endpoint and ANCOVA model for the analysis of secondary endpoints. For a linear model, the two approaches yield the same results.

Multiplicity Adjustment: There was no multiplicity issue in both studies.

In the CHOC study, the primary efficacy variable was compared between Cystadrops and CH 0.01% at Day 90 at a two-sided significance level of 5%. Furthermore, since no formal multiple comparison procedure for testing the secondary efficacy variables was specified, p-values and confidence intervals reported for testing the secondary efficacy variables were intended for descriptive use only. In OCT-1 study, the primary and key secondary efficacy variables were analyzed descriptively.

Handling Missing Data: There was no or minimal missing data issue in both studies.

Per the applicant, the IVCM procedure may not have been feasible in younger children (<18 years of age), and as such, only patients that underwent the IVCM procedure were included in the primary analysis.

In the OCT-1 study, all eight subjects (16 eyes) completed the study and had efficacy data throughout the study. In the CHOC study, on the other hand, 19 of 31 subjects were young children and 9 of the 19 young children (4 in Cystadrops and 5 in CH 0.10%) for whom an IVCM total score could not be measured at baseline were not included in the primary efficacy analysis.

Additionally, two subjects in the CHOC study (one in each treatment group) were also excluded from the primary analysis due to missing total IVCM score. Note that the total IVCM score was considered missing if the IVCM data for any one of the seven layers of the cornea was missing. It should be further noted that although IVCM score could not be measured for 9 of the 19 young children in the CHOC study, these subjects had complete data for the secondary efficacy variables.

Reviewer's Remark:

To assess the impact of unobserved/missing IVCM data (including unobserved baseline IVCM data) on the overall conclusion, the reviewer performed sensitivity analysis. The sensitivity analysis was performed by imputing unobserved/missing IVCM data for a subject by the average IVCM data from all subjects with available IVCM data. Imputation was done for each layers of the cornea separately as follows: (i) Imputation ***for baseline data*** *was done by age group (young children versus adults) regardless of the treatment assignment and (ii) Imputation* ***for post-baseline data*** *was done by age and treatment group; that is, unobserved IVCM data for young subjects in the Cystadrops group were imputed only from young subjects in the Cystadrops group with available data.*

Once the imputation was done within each layer of the cornea, the total IVCM was calculated by summing across the seven layers. The results of the sensitivity analysis are presented in Table 10. As shown, except for minor numerical differences, the overall efficacy conclusion remains unchanged.

Sample Size Justification for the Pivotal CHOC Study

The applicant stated that the sample size required for the pivotal CHOC study was determined based on the total IVCM data observed in the OCT-1 pilot study. In the OCT-1 study, as shown in Figure 3, the mean change (standard deviation) in the total IVCM score at Day 90 was -3.2 (1.8). Using this data and assuming no reduction in the CH 0.10% group at Day 90, a sample size of 12 subjects would provide 90% power to detect a treatment difference (*Cystadrops minus CH 0.01%*) in the mean change in total IVCM score at Day 90 of -3.0 unit with a standard deviation of 2 unit at a two-sided significance level of 0.05.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition

A total of 8 subjects (16 eyes) were enrolled in OCT-1 study and all subjects (eyes) completed the study. In the CHOC study, a total of 32 subjects were enrolled (15 subjects to Cystadrops and 17 subjects to CH 0.10%). Per the study report, one subject randomized to CH 0.10% was reported as lost to follow-up after randomization and no information on study product administration was collected for this subject prior to drop-out. Thus, a total of 31 subjects (62 eyes) in this study underwent all study assessments and completed the study.

Demographic and Baseline Disease Characteristics

The summaries of the demographic and baseline disease characteristics for all randomized subjects who received at least one dose of study medication are shown in Table 2. As shown, most subjects in both studies were Female (75% in OCT-1 and 52% in CHOC). The average age at the time of study inclusion was about 12 years (range: 7-21 years) in OCT-1 study and 17 years (range: 3-63 years) in CHOC study. Most subjects in both studies were under 18 years (88% in OCT-1 and 61% in CHOC).

In the CHOC study, 19 of 31 subjects were young children (<18 years) and 9 of the 19 young children did not have baseline IVCM measurement (7 were under 12 years and 2 were from 12 to < 18 years). Table below show the age of the 9 subjects with no IVCM data at baseline. In the OCT-1 study, all eight subjects had baseline IVCM measurement.

	Cystadrops				CH 0.10%				
Subject ID	(b) (6)								
Age	2	3	10	12	3	4	8	11	12

In terms of baseline disease characteristics, subjects in OCT-1 and CHOC studies had 11 years and 15 years duration of the disease at study entry, respectively. Three subjects in OCT-1 and six subjects in CHOC had renal transplantation prior to the study.

Table 2: Summary of demographic and baseline disease characteristics
(Randomized Subjects [a])

		OCT-1	CHOC		
		All Subjects (N = 8)	Cystadrops (N = 15)	CH 0.10% (N = 16)	All Subjects (N = 31)
Gender, N (%)	Male Female	2 (25.0) 6 (75.0)	7 (46.7) 8 (53.3)	8 (50.0) 8 (50.0)	15 (48.4) 16 (51.6)
Age at time of [b] inclusion (years)	Mean (SD) Median Min - Max	12.1 (4.6) 11.5 7.0 - 21.0	19.2 (15.5) 13.0 2.0 - 62.0	15.1 (10.3) 11.5 3.0 - 36.0	17.1 (13.0) 13.0 2.0 - 62.0
Age (class) at inclusion, N (%)	Child (< 12 years) Adolescent (12 to < 18 years) Adult	4 (50.0) 3 (37.5) 1 (12.5)	5 (33.3) 3 (20.0) 7 (46.7)	8 (50.0) 3 (18.8) 5 (31.3)	13 (41.9) 6 (19.4) 12 (38.7)
Stratum, N (%)	No IVCM IVCM/<12 IVCM/12 to <18 years IVCM/Adult	0 4 (50.0) 3 (37.5) 1 (12.5)	4 (26.7) 2 (13.3) 2 (13.3) 7 (46.7)	5 (31.3) 4 (25.0) 2 (12.5) 5 (31.3)	9 (29.0) 6 (19.4) 4 (12.9) 12 (38.7)

			OCT-1	CHOC		
			All Subjects (N = 8)	Cystadrops (N = 15)	CH 0.10% (N = 16)	All Subjects (N = 31)
Duration of the disease at study entry (years)	Mean (SD) Median Min – Max		10.6 (4.2) 10.0 6.0 - 19.0	15.9 (11.0) 12.7 0.775 - 33.9	13.8 (10.8) 9.20 0.695 - 35.5	14.8 (10.8) 11.6 0.695 - 35.5
Age at diagnosis of the disease (months)	Mean (SD) Median Min - Max		17.5 (10.8) 15.5 0.0 - 38.0	38.4 (89.3) 16.0 5.00 – 360	15.5 (11.1) 15.5 5.00 - 46.0	26.6 (62.6) 16.0 5.00 - 360
Renal transplantation	No Yes		5 (62.5) 3 (37.5)	12 (80.0) 3 (20.0)	13 (81.3) 3 (18.8)	25 (80.6) 6 (19.4)
	Age at the time of renal transplantation (years)	Mean (SD) Median Min - Max	10.3 (1.5) 10.0 9.0 – 12.0	14.7 (7.77) 17.0 6.00 - 21.0	16.3 (2.08) 17.0 14.0 - 18.0	15.5 (5.17) 17.0 6.00 - 21.0

[a] Included all randomized subjects who received at least one dose of study drug; [b] Based on reviewer analysis.
Source: Table 2.7.3-2 and Table 2.7.3-3 of Applicant's Summary of Clinical Efficacy

Per the study reports, in both studies, most subjects used systemic cysteamine (100% in OCT-1 and 94% in CHOC) for the treatment of cystinosis prior to the study. Subjects in the CHOC study on average used systemic cysteamine for about 10 years and topical cysteamine for 12 years prior to the study.

The table below shows the baseline summary data for the key efficacy variables in the two studies: total IVCM, CCCS, CT, and photophobia. As shown, the mean baseline values for these variables in the CHOC study were comparable between the treatment groups except for CT. Regarding CT, Cystadrops treated eyes had slightly higher mean baseline CT compared to CH 0.10% treated eyes (275 µm versus 260 µm).

	Summary	OCT-1	Cystadrops	CH 0.10%
Total IVCM	N Mean (SD) Median Min - Max	16 11.4 (2.94) 11.0 7.0 – 18.0	20 10.6 (4.18) 10.85 3.2 - 19.0	20 10.8 (3.47) 10.75 4.2 - 16.2
CCCS	N Mean (SD) Median Min - Max	16 2.9 (0.13) 3.0 2.75 – 3.00	30 2.26 (0.56) 2.25 1.50 - 3.00	31 1.98 (0.50) 2.00 1.00 - 3.00
CT (µm)	N Mean (SD) Median Min - Max	16 306.4 (98.87) 266.0 200.00 – 531.00	30 275 (159) 245 46 – 580	31 260 (167) 180 42 - 558
Photophobia	N Mean (SD) Median Min - Max	16 2.5 (0.89) 2.5 1.0 – 4.0	30 1.87 (1.17) 2.0 0.0 - 4.0	31 1.68 (1.05) 2.0 0.0 - 4.0

Note: Descriptive summaries in the table were created by treating measurements of two eyes as independent

3.2.4 Efficacy Results and Conclusions

In this section, the results of the primary and secondary efficacy variables for both studies are presented and discussed.

Analysis of Primary Efficacy Variable: Change in IVCM

In the pivotal CHOC study, 31 subjects (62 eyes) underwent all study assessments and completed the study (15 subjects [30 eyes] in Cystadrops and 16 subjects [32 eyes] in CH 0.10%).

Table 3 below shows the number of subjects with observed (and missing in parenthesis) total IVCM data at each visit. As shown, in the Cystadrops group, 8 eyes from four young children had no baseline total IVCM score and two eyes from one adult subject had no total IVCM score because of missing score in one of the seven layers of the cornea. Similarly, in the CH 0.10% group, 10 eyes from five young children and two eyes from one adult had no baseline total IVCM measures for all layers of the cornea. Thus, there were a total of 10 evaluable subjects (20 eyes) in each treatment group for the analysis of the primary efficacy variable.

Table 3: Number of eyes with observed (unobserved/missing) IVCM data over time (Randomized Subjects)

Visit	Age Group	Cystadrops (N=30)	CH 0.10% (N = 32)	Total (N = 62)
Day 1 (Baseline)	< 18 Years	8 (8)	12 (10)	20 (18)
	≥ 18 Years	12 (2)	8 (2)	20 (4)
	Total	**20 (10)**	**20 (12)**	**40 (22)**
Day 30	< 18 Years	8 (8)	12 (10)	20 (18)
	≥ 18 Years	12 (2)	6 (4)	18 (6)
	Total	**20 (10)**	**18 (14)**	**38 (24)**
Day 90	< 18 Years	8 (8)	11 (11)	19 (19)
	≥ 18 Years	12 (2)	6 (4)	18 (6)
	Total	**20 (10)**	**17 (15)**	**37 (25)**

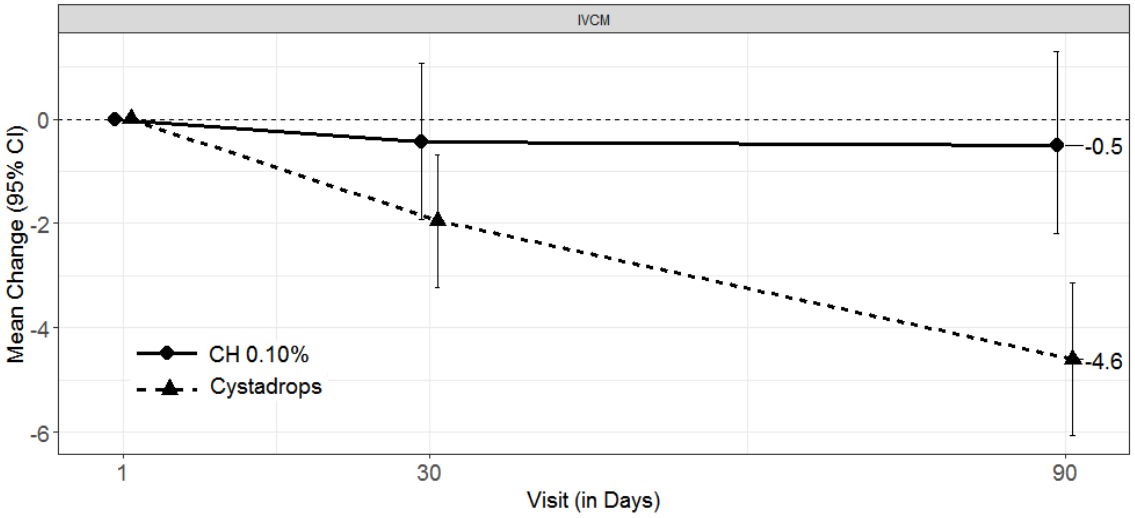
Note: Numbers in parenthesis are number of subjects with no IVCM data

It should be noted that in the Cystadrops group all 20 evaluable eyes had total IVCM data throughout the study whereas, in the CH 0.10% group, two eyes form one adult subject did not have post-baseline total IVCM data at Days 30 and 90 and one eye from another young child did not have total IVCM data at Day 90.

In Figure 1 below, the mean change in the total IVCM from baseline (Day 1) at each visit based on the 20 evaluable eyes are presented for each treatment group (See Figure 14 for the profile of each subject). As shown, at Day 90, Cystadrops treated eyes had an average reduction of about 5-unit compared to a half-unit reduction for CH 0.10% treated eyes. Also, as shown in appendix Table 8, eyes treated with Cystadrops yielded a 40% average reduction in the total IVCM score from baseline at Day 90 compared to a 0.7% reduction for eyes treated with CH 0.10%.

The applicant performed treatment comparison between Cystadrops and CH 0.10% with respect to the change in the total IVCM at Day 90 using GEE model. The model included treatment as a factor and baseline IVCM score as a covariate. To account for the correlation between eyes of the same subject, the applicant used an autoregressive (AR [1]) covariance-structure. As shown in Figure 13, a strong correlation existed between measurements of the two eyes in the total IVCM score at each study visit.

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



Source: Appendix Table 8

Table 4 below shows the summary of the total IVCM score at baseline, Day 90, and the change from baseline at Day 90. The table also shows the treatment difference (*Cystadrops minus CH 0.10%*) and the corresponding 95% confidence interval (CI) including the p-value based on the GEE model.

Based on the GEE model, Cystadrops was determined superior to CH 0.10% in the reduction of corneal cystine crystal density as measured by the total IVCM from baseline at Day 90. At Day 90, subjects in the Cystadrops group yielded an average reduction of 4.6 units compared to 0.5 units in the CH 0.10% group. 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 to 5.58); p-value < 0.001).

Table 4: Summary of mean change in IVCM from baseline at Day 90
(Full Analysis Set)

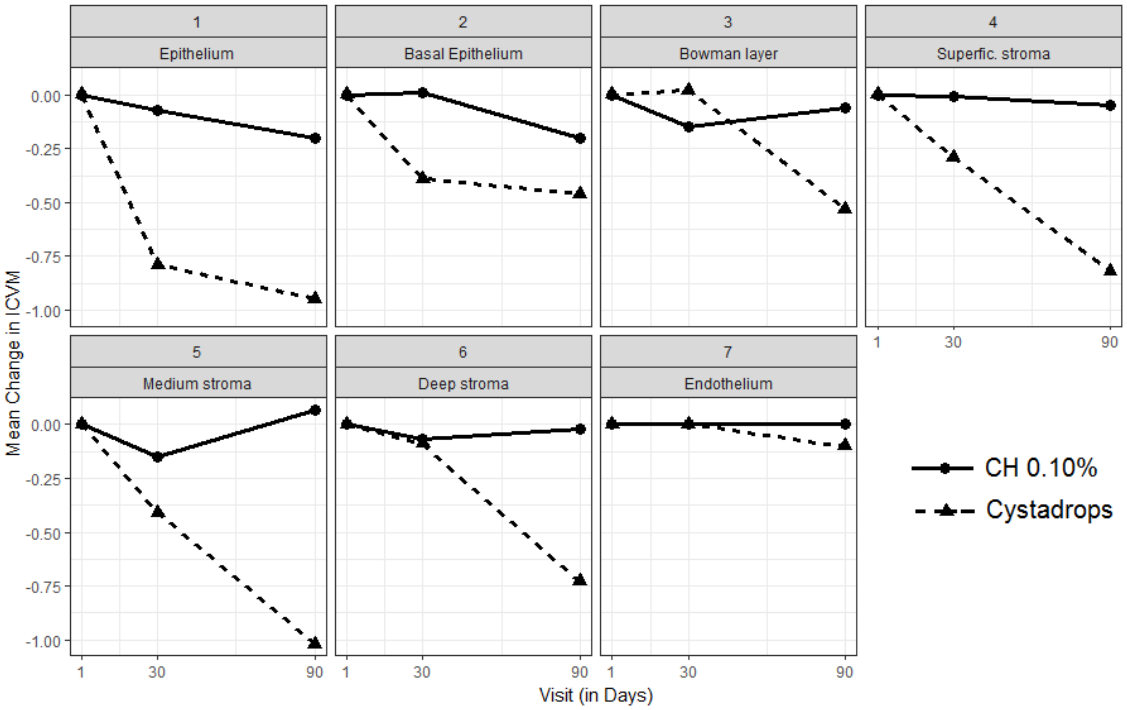
Visit	Summary	Cystadrops	CH 0.10%
Baseline (Day 1)	n Mean (SD) Median Range	20 10.6 (4.18) 10.85 (3.2, 19.0)	20 10.8 (3.47) 10.75 (4.2, 16.2)
Day 90	n Mean (SD) Median Range	20 6.04 (2.08) 5.9 (2.0, 9.6)	17 9.81 (3.81) 10.0 (5.0, 17.8)
Change from baseline to Day 90	n Mean (SD) Median Range	20 -4.6 (3.12) -4.13 (-11.0, -0.6)	17 -0.45 (3.38) -1.2 (-7.6, 6.5)
	Difference in LS Means (95% CI) [1] p-value	-3.84 (-5.58, -2.11) <0.001	--
	Difference in LS Means (95% CI) [2] p-value	-3.82 (-5.77, -1.87) <0.001	--
	Difference in LS Means (95% CI) [3] p-value [4]	-3.83 (-5.70, -1.56) 0.008	--

[1] Applicant analysis based on GEE model; [2] Reviewer analysis based on ANCOVA model accounting for correlation between two eyes (SAS Proc Mixed). [3] Reviewer analysis based on bootstrap; [4] P-value based on 500 permutation sample.

To assess the robustness of the results from the GEE model, the reviewer also analyzed the primary efficacy variable using: (i) ANCOVA model based on bootstrap samples, (ii) ANCOVA model accounting for correlation between two eyes (using SAS Proc Mixed), and (iii) ANCOVA model taking the average values of the two eyes. As shown in Table 4 above, except for minor numerical differences, the bootstrap approach and the ANCOVA mixed-model approach yielded comparable results to the GEE model.

To assess the contribution of the seven layers of the cornea to change in the total IVCM score, Figure 2 below displayed the change in IVCM score over time for each layer of the cornea. As shown, at Day 90, Cystadrops treated eyes yielded numerically better reduction in corneal cystine crystal density in each layers of the cornea compared to CH 0.10% treated eyes and it appeared that larger reduction was achieved in the epithelium and the three levels of stroma of the cornea.

Figure 2: Mean change in IVCM score from baseline over time by layers of the cornea (Full Analysis Set)

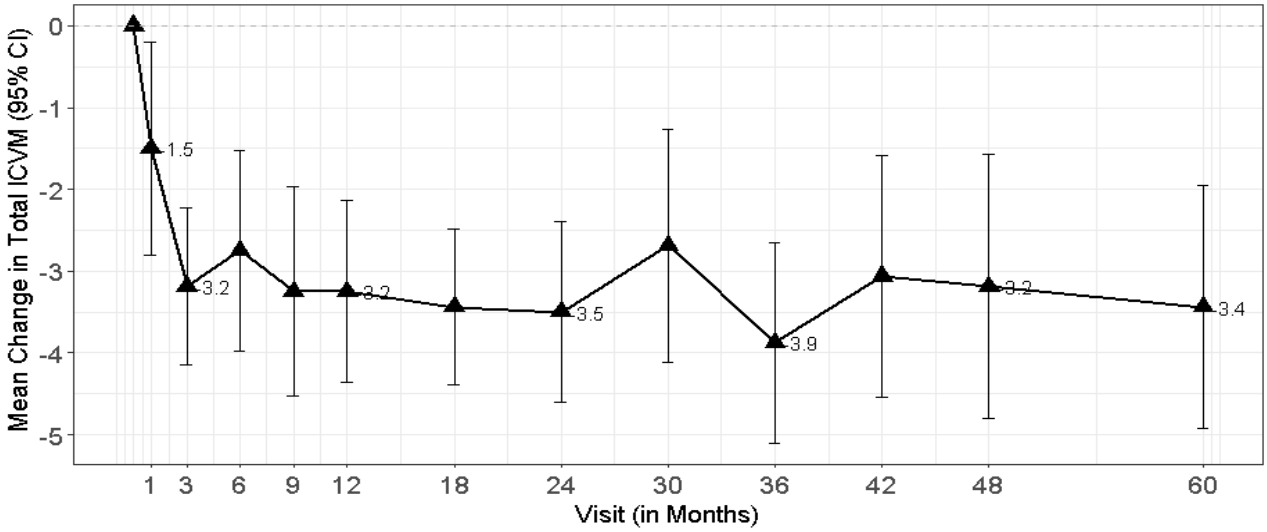


The reduction in the total IVCM score observed in CHOC study was supported by the single arm OCT-1 study. A total of 8 subjects (16 eyes) were enrolled in the OCT-1 study and all subjects in this study received Cystadrops for 60 months after subjects had received CH 0.10% for one month during the run-in period. During the treatment period (Day 1 to Month 60), subjects were to receive 3-4 instillations per day per eye on average. For example, at Day 1 and Month 1, subjects received 4 instillations per day per eye and approximately three instillations per day per eye Month 3 onwards.

Figure 3 below displays the mean change in the total IVCM score from baseline at each visit in the OCT-1 study (vertical bars represent 95% CI). As shown, Cystadrops showed a significant reduction in the total IVCM score from baseline through Month 3 (as in the CHOC study). The reduction stabilized afterwards through Month 60. At Month 3, a mean reduction of 3.2 unit (95% CI: 2.2 to 4.1) from baseline was observed. The average percent reduction at Day 30 was about 12% and an

average reduction of about 30% was achieved from Month 3 through Month 60 in 7 of the 8 subjects who had a median dosing regimen of 3 drops/eye/day (See Table 9). The profile for each subject is shown in Appendix Figure **15**.

Figure 3: Mean change in total IVCM from baseline by visit (OCT-1 Study)
(Full Analysis Set)



Source: Appendix Table 9

Analysis of Secondary Efficacy Variables

i) Cystinosis Corneal Crystal Score (CCCS)

In both studies, CCCS was measured by the investigator during a slit lamp examination in a 0 to 3 scale in 0.25 increments: *0 (clarity at the center) to 3 (greatest recognizable crystal density)*. A decrease in the CCCS score over time signals an improvement in this parameter. In the CHOC study, subjects in the Cystadrops and CH 0.10% groups had a baseline CCCS score of 2.3 and 2.0 units, respectively. The baseline scores were comparable.

Figure 4: Mean change (95% CI) in CCCS by visit
(Full Analysis Set)

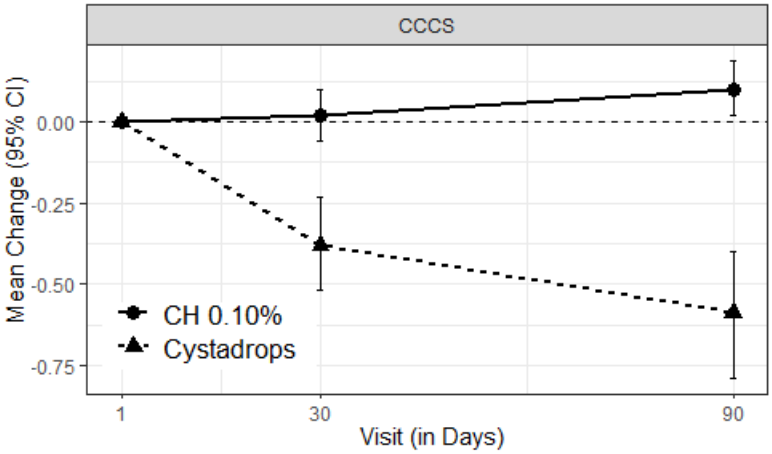


Figure 4 displayed the mean change in CCCS over time. As shown, Cystadrops treated eyes demonstrated a significant reduction in CCCS compared to CH 0.10% treated eyes throughout the study.

For example, as shown in Figure 5 below, 60% and 30% of Cystadrops treated eyes showed at least half- and one-unit improvement in CCCS from baseline at Day 90, respectively, compared to 0% of CH 0.10% treated eyes.

Figure 5: Cumulative distribution of change in CCCS from baseline at Day 90
(Full Analysis Set)

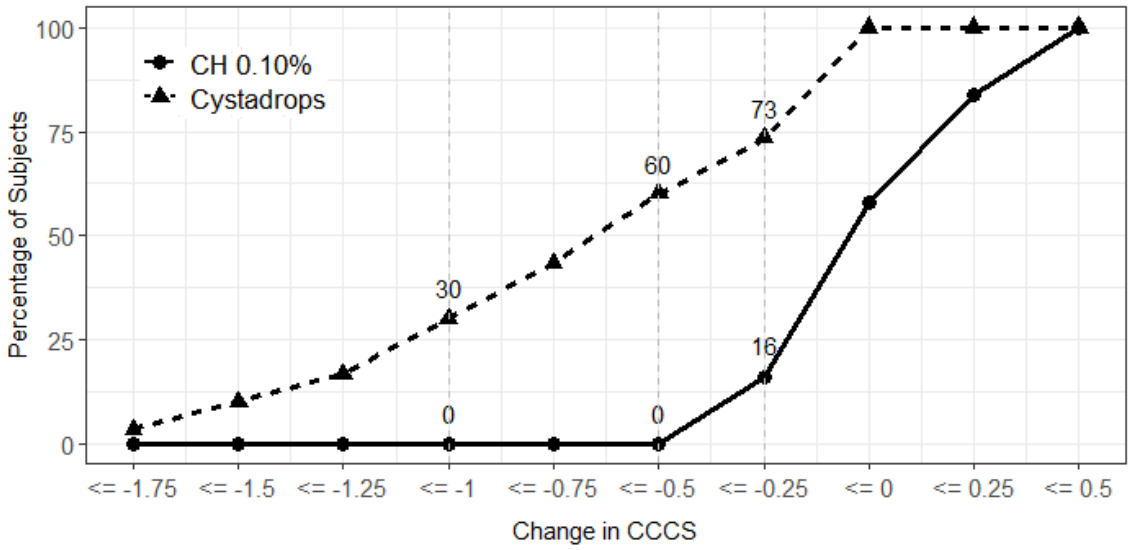


Table 5 below shows the treatment comparison in the mean change in CCCS at Day 90. As shown, at Day 90, subjects in the Cystadrops group yielded an average reduction of 0.6 units compared to a worsening in the CH 0.10% group by 0.1-unit. The treatment difference (*Cystadrops minus CH 0.10%*) in the mean reduction in CCCS at Day 90 was 0.57 (95% CI: (0.24, 0.91); p-value = 0.0015).

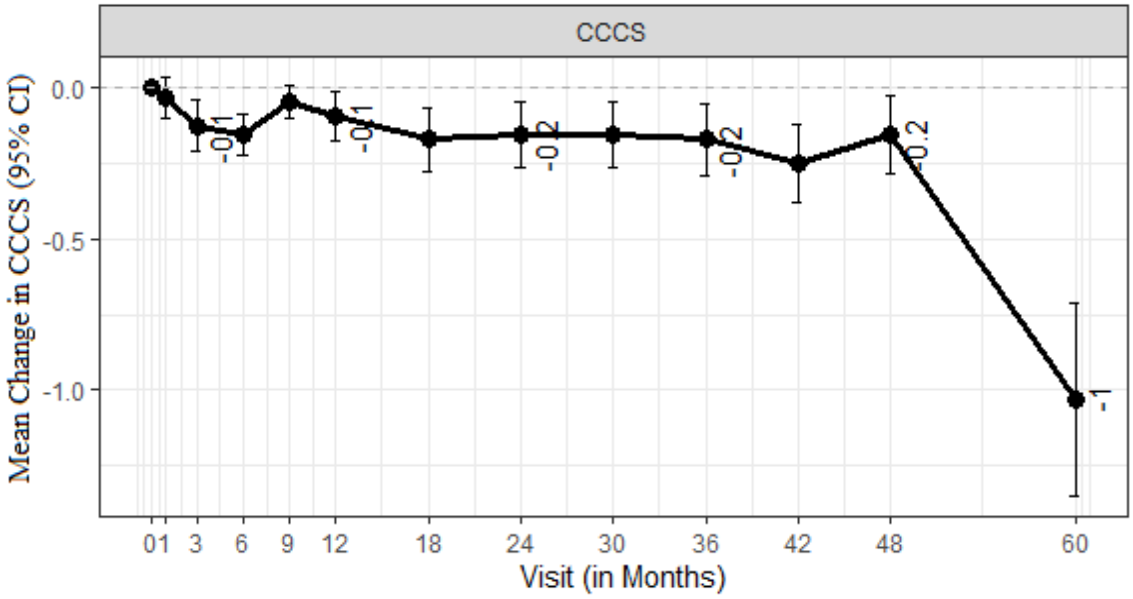
Table 5: Summary of change in CCCS from baseline at Day 90
(Full Analysis Set)

Visit	Summary	Cystadrops®	CH 0.10%
Baseline (Day 1)	n Mean (SD) Median Range	30 2.26 (0.56) 2.25 (1.50, 3.00)	31 1.98 (0.50) 2.00 (1.00, 3.00)
Day 90	n Mean (SD) Median Range	30 1.67 (0.73) 1.75 (0.50, 3.00)	31 2.09 (0.52) 2.00 (1.00, 3.00)
Change from baseline to Day 90	n Mean (SD) Median Range	30 -0.59 (0.52) -0.5 (-1.75, 0.00)	31 0.10 (0.24) 0.00 (-0.25, 0.50)
	Difference in LS Means (95% CI) [1] p-value	-0.57 (-0.91, -0.24) 0.0015	--
	Difference in LS Means (95% CI) [2] p-value [3]	-0.68 (-0.95, -0.38) <0.001	

[1] Applicant analysis based on ANCOVA model accounting for correlation between two eyes.
[2] Reviewer analysis based on bootstrap; [3] P-value based on permutation test.

In Figure 6 below, the mean change in CCCS in the Cystadrops group in the single arm OCT-1 study is displayed. As in the CHOC study, Cystadrops treated eyes in OCT-1 study demonstrated a reduction in CCCS from baseline over time although the magnitude of reduction in the OCT-1 study was smaller than in the CHOC study.

Figure 6: Mean change (95% CI) in CCCS by visit (OCT-1 Study)



Reviewer's Remark:

*The approval of Cystaran® in the US (NDA 200740) for the same indication was based on the primary efficacy variable of: "**The response rate of eyes that had a reduction of at least 1 unit in CCCS at some time point during the study when baseline CCCS ≥1, or a lack of an increase of more than 1 unit in CCCS throughout the study when baseline CCCS <1**".*

Similar analysis in the current submission resulted in a 30% response rate through 3 months for Cystadrops compared to 0% for the control arm CH 0.10% in the CHOC study and 63% (5 out of 8 subjects) through year 5 for Cystadrops in the OCT-1 study. It should be noted that all subjects in the current submissions had a baseline CCCS of ≥1.0.

ii) Crystal Thickness

The crystal thickness (CT), used to measure the depth of the cystine crystal deposits in the cornea, is summarized in this section for each treatment group. Figure below shows the mean change in CT over time. A decrease in CT over time signals an improvement in this parameter. In the CHOC study, subjects in the Cystadrops and CH 0.10% groups had a baseline CT of 275 µm and 260 µm, respectively. The baseline CT was slightly higher in the Cystadrops group.

Figure 7: Mean change in Crystal Thickness over time
(Full Analysis Set)

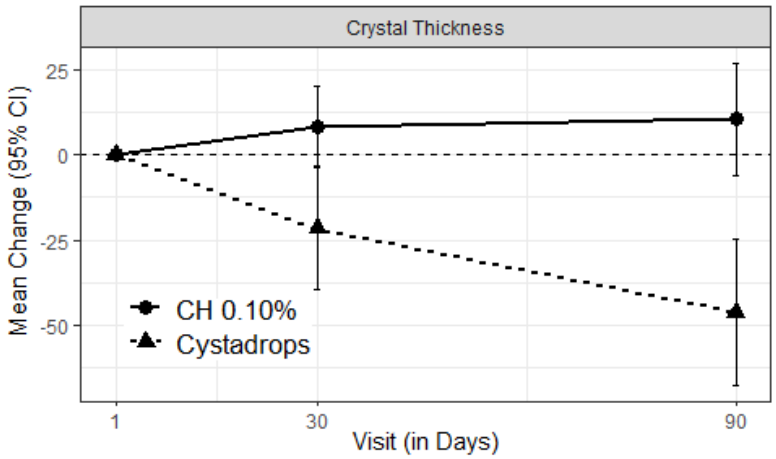


Figure 7 shows the mean change in crystal thickness over time.

As shown, Cystadrops treated eyes demonstrated a significant reduction in CT compared to CH 0.10% treated eyes throughout the study.

Table 6 below shows the treatment comparison in the mean change in CT at Day 90. As shown, Cystadrops treated eyes yielded substantial reduction in CT compared to CH 0.10% treated eyes from baseline at Day 90. At Day 90, subjects in the Cystadrops group yielded an average CT reduction of 46 µm compared to a worsening in the CH 0.10% group from baseline by about 11 µm. The treatment difference (*Cystadrops minus CH 0.10%*) in the mean reduction in CT at Day 90 was 53.9 (95% CI: (19.9 µm, 87.9 µm); p-value = 0.0031).

Table 6: Mean change in CT score from baseline at Day 90
(Full Analysis Set)

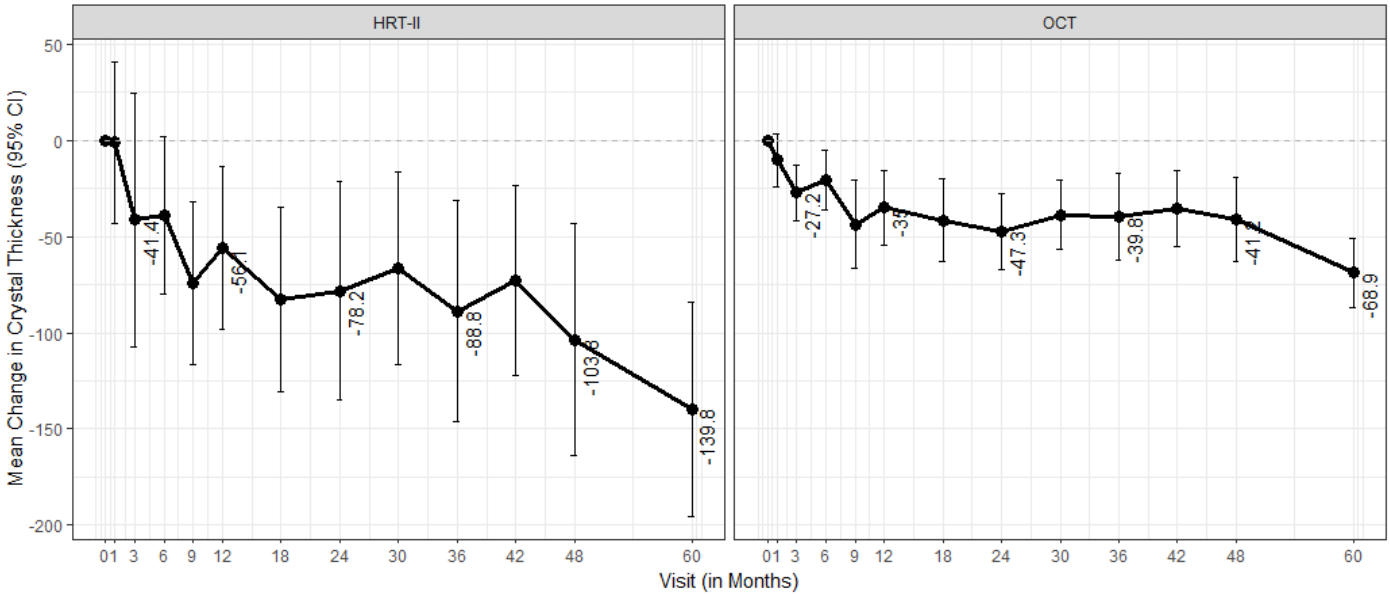
Visit	Summary	Cystadrops®	CH 0.10%
Baseline (Day 1)	n Mean (SD) Median Range	30 275 (159) 245 (46, 580)	31 260 (167) 180 (42, 558)
Day 90	n Mean (SD) Median Range	28 241 (133) 270 (47, 470)	 259 (174) 207 (0, 55)
Change from baseline to Day 90	n Mean (SD) Median Range	28 -46.3 (55.33) -34.0 (-230, 84)	29 10.59 (43.55) 20 (-95, 83)
	Difference in LS Means Diff. (95% CI) [1] p-value	-53.91 (-87.89, -19,92) 0.0031	--
	Difference in LS Means Diff. (95% CI) [2] p-value [3]	-52.07 (-81.41, -17.73) 0.0070	--

[1] Applicant analysis based on ANCOVA model accounting for correlation between two eyes.
[2] Reviewer analysis based on bootstrap; [3] P-value based on permutation test.

Figure 8 below displays the mean change in CT in the Cystadrops group in the single arm OCT-1 study. It should be noted that CT was measured in this study based on two different methods: using

HRT-II and OCT. In both methods, Cystadrops treated eyes in OCT-1 study demonstrated a reduction in CT from baseline over time. At Month 3 (Day 90), the magnitude of reduction using the HRT-II method in the OCT-1 study is very similar to in the CHOC study (46 µm versus 41 µm).

Figure 8: Mean change in CT score from baseline over time (OCT-1)
(Full Analysis Set)



iii) Photophobia

Photophobia, considered as one of the clinical symptoms of cystinosis, was assessed on a 0 to 5 scale based on an objective assessment by the investigator: 0 (absence) to 5 (extreme). A decrease from baseline in photophobia score over time signals an improvement in this parameter.

In the CHOC study, subjects in the Cystadrops and CH 0.10% groups, respectively, had a baseline average photophobia score of 1.9 and 1.7 unit. The baseline scores were comparable.

Figure 9: Mean change in photophobia score over time
(Full Analysis Set)

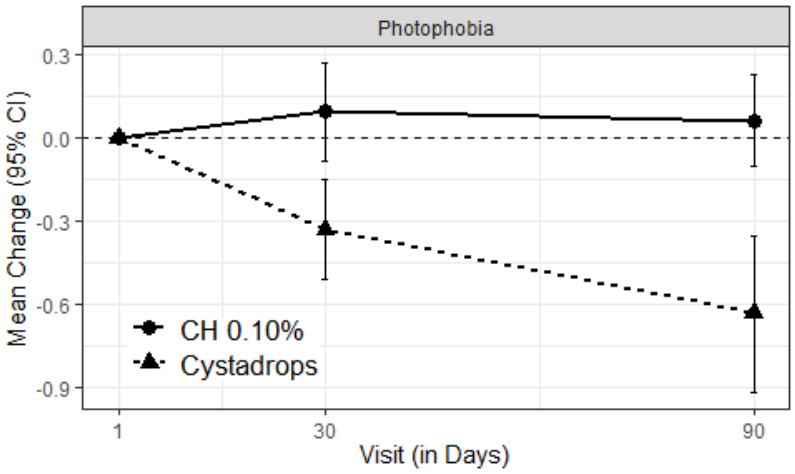


Figure 9 shows the mean change in photophobia score over time.

As shown, Cystadrops treated eyes demonstrated a larger reduction in Photophobia score than CH 0.10% treated eyes throughout the study.

For example, as shown in Figure 10, 47% and 17% of Cystadrops treated eyes showed at least 1- and 2-unit improvement in photophobia score from baseline at Day 90, respectively, compared to 6% and 0% of CH 0.10% treated eyes.

Figure 10: Cumulative distribution of change in photophobia from baseline at Day 90 (Full Analysis Set)

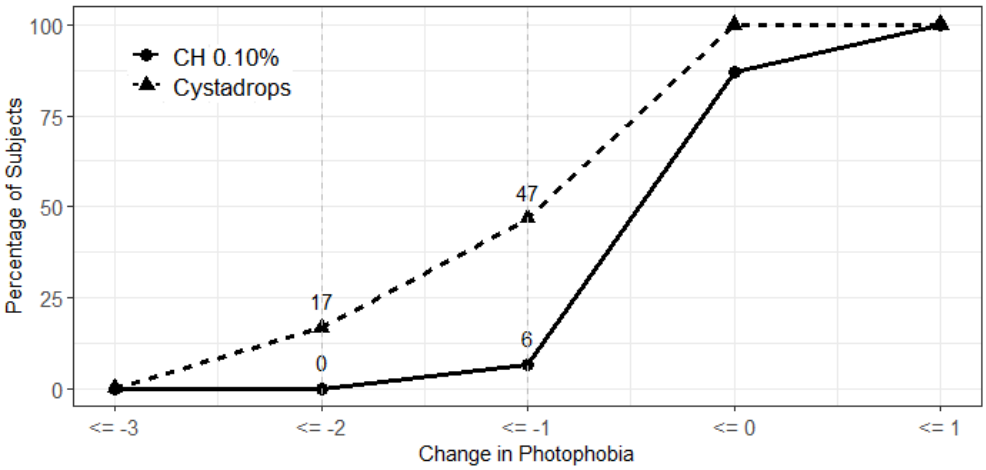


Table 7 below shows the treatment comparison in the mean change in Photophobia score at Day 90. As shown, at Day 90, Cystadrops treated eyes had an average reduction of 0.6 unit compared to a slight worsening from baseline in the CH 0.10% group. The treatment difference (*Cystadrops minus CH 0.10%)* in the mean reduction in photophobia score at Day 90 was 0.68 (95% CI: (0.23 to 1.14); p-value=0.0048).

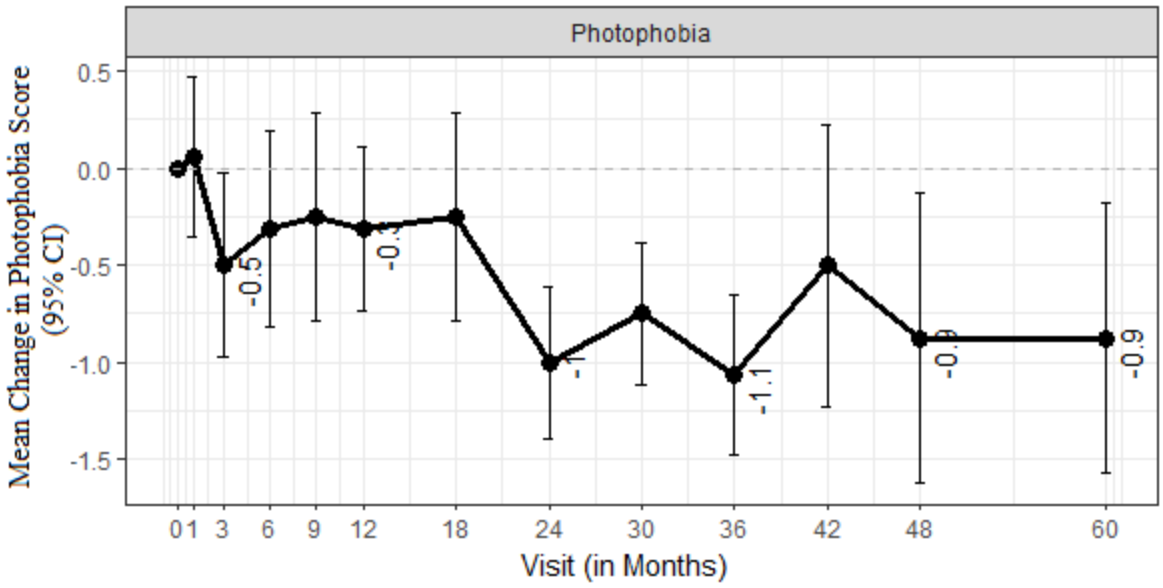
Table 7: Summary of change in Photophobia score from baseline at Day 90 (Full Analysis Set)

Visit	Summary	Cystadrops®	CH 0.10%
Baseline (Day 1)	n Mean (SD) Median Range	30 1.87 (1.17) 2.0 (0.0, 4.0)	31 1.68 (1.05) 2.0 (0.0, 4.0)
Day 90	n Mean (SD) Median Range	30 1.23 (1.17) 1.0 (0.0, 3.0)	32 1.81 (1.20) 2.0 (0.0, 4.0)
Change from baseline to Day 90	n Mean (SD) Median Range	30 -0.63 (0.76) 0.0 (-2.0, 0.0)	31 0.06 (0.44) 0.0 (-1.0,1.0)
	Difference in LS Means Diff. (95% CI) [1] p-value	-0.68 (-1.14, -0.23) 0.0048	--
	Difference in LS Means Diff. (95% CI) [2] p-value [3]	-0.68 (-1.13, -0.28) 0.0060	--

[1] Applicant analysis based on ANCOVA model accounting for correlation between two eyes.
[2] Reviewer analysis based on bootstrap; [3] P-value based on permutation test.

Figure 11 below displays the mean change (95% CI) in Photophobia score over time in the Cystadrops group in the single arm OCT-1 study. As shown, Cystadrops treated eyes in OCT-1 study displayed a half to a unit reduction in photophobia score from baseline over time. At Month 3 (Day 90), the magnitude of reduction in the OCT-1 study is very similar to in the CHOC study (0.5 versus 0.6 unit).

Figure 11: Mean change in Photophobia score from baseline over time (OCT-1)



Supporting Efficacy Evidence Based on Published Data

To supplement the efficacy data in the CHOC and OCT-1 studies, the applicant also submitted nine published literatures on other ocular formulations containing the active substance, cysteamine hydrochloride. The efficacy findings in these literatures are summarized below.

Study 1 (USA): Kaiser-Kupfer et al. (1990)

Study 1 was a randomized, double-masked, placebo-controlled study conducted in the United States. In the study, 29 patients 2 month to 31 years of age (18 patients < 4 years and 11 patients 4-31 years) with nephropathic cystinosis were enrolled and received one drop of study drug (cysteamine eye drops [0.1% or 0.5%]) in one eye or placebo in the other eye every waking hour for 47 months (from November 1985 to September 1989). It should be noted that, for some patients, the cysteamine concentration was changed to 0.5% during the trial.

A difference in corneal crystals density in the two eyes and a decrease in the better eye from previous visit was examined by three clinical and three photographic observers. The level of corneal crystals density was scored using corneal cystine crystals score (CCCS) in a 4-point scale (0 to 3 in 0.125 increment).

In the study, four patients discontinued prior to study completion. Per the study result, 10 cysteamine-treated eyes (eight under 4 years and two 4-31 years) of the remaining 25 patients demonstrated a difference in corneal crystals density in the two eyes and a decrease in the better eye from previous visit. There were no marked differences between the two eyes in 15 of the patients.

Study 2 (United Kingdom): MacDonald et al. (1990)

Study 2 was a randomized, double-masked, and placebo-controlled study designed to determine whether topical cysteamine 0.3% drops applied in one eye 4 times per day would be effective compared to placebo (normal salin in the fellow eye) in reducing crystal formation within the cornea of patients with nephropathic cystinosis. In the study, four patients (3 female and 1 male) 33 month to 21 years of age were examined at 2-month intervals for seven months. In the study, three observers independently ranked the clinical appearance of corneal crystals in the two eyes as better, worse, or the same throughout the study period.

All patients completed the study and, in this study, no appreciable difference in the number of crystals was seen in the corneas of the treated and untreated eyes.

Study 3 (United Kingdom): Bradbury et al. (1991)

Study 3 was a randomized, double-masked, and placebo-controlled study designed to determine whether topical cysteamine 0.2% drops would be effective compared to placebo (normal saline) in reducing corneal cysteine crystal score (CCCS) in patients with cystinosis. In the study, five patients 6 to 12 years of age were examined monthly for six months and received topical cysteamine 0.2% six times a day in one eye and placebo in the other eye as a control. In the study, two independent observers independently scored the crystal density in a 5-point scale (0 to 4 in 0.5 increments). Also, subjective assessments were made in the study to evaluate photophobia, pain, blepharospasm, and visual acuity.

Per the study, all cystamine-treated eyes showed at least 0.5-unit improvement in CCCS. Also, all topical cysteamine-treated eyes showed a subjective improvement in Photophobia, pain, blepharospasm, and visual acuity.

Study 4 (USA): Tsilou et al. (2003)

Study 4 was a randomized and double-masked study designed to evaluate the safety and efficacy of a new topical cysteamine formulation (*0.55% cysteamine hydrochloride solution with monosodium phosphate 1.85%, disodium EDTA 0.10%, and benzalkonium chloride 0.01%*) compared to a standard formulation (*0.55% cysteamine hydrochloride solution with benzalkonium chloride 0.01%*) for the treatment of corneal cystine crystals in patients with cystinosis. In the study, 16 subjects 2-11 years of age with cystinosis who had never received topical cysteamine and whose corneal cystine crystal score (CCCS) was >1.00 were enrolled to assess the proportion of subjects with a reduction in CCCS of ≥ 1-unit. In the study, subjects received one drop of the new formulation in one eye and the standard formulation in the fellow eye every waking hour and CCCS was scored by two independent observers in a 4-point scale (0 to 3 with 0.25 increments) every 3 months for 12 months.

In the study, subjects had a baseline CCCS of 1.25 units and an average age of 6 years. One subject discontinued the study early. At year 1, 47% of eyes treated with the standard formulation achieved ≥ 1-unit reduction in CCCS from baseline compared to 7% of eyes treated with the new formulation. The median change in CCCS in the standard formulation was -0.75 compared to 0.0 for the new formulation (p=0.0005, Wilcoxon signed rank test).

Study 5 (Saudi Arabia): Al-Hemidan et al. (2017)

Study 5 was prospectively designed to evaluate the efficacy of cysteamine 0.55% eye drops in the treatment of corneal cystine crystal deposits in patients with nephropathic cystinosis. In the study, 32 patients 8 months to 19 years of age were enrolled during the period of 2004 to 2012 and received one drop of Cysteamine 0.55% every two hours while awake in both eyes. The main efficacy evaluation was based on photophobia and resolution of corneal cysteine crystals. Photophobia was graded in a 4-point scale (*Grade 0: none [no photophobia]; 1: mild [photophobia in bright light]; 2: moderate [photophobia in room light]; and 3: severe [photophobia in dim light]*) and corneal cysteine crystals were also graded in a 4-point scale (*Grade 0 = none; 1 = 1-10 crystals/mm^2; 2 = 11-50 crystals/mm^2, and 3 = >50 crystals/mm^2*).

In the study, a total of 32 patients were enrolled (13 male and 19 female). The mean age of patients was 8 years. At baseline, 14, 9, and 9 patients had a photophobia grade of 0, 1, and 2, respectively. All patients had corneal crystal at baseline: 8, 5, and 19 patients had grade 1, 2, and 3 crystals, respectively.

Among the 14 patients with no photophobia at baseline, 10 patients did not increase in symptoms whereas 4 patients progressed to grade 1. Among the 18 patients with photophobia at baseline, 7 (39%) patients showed improvement from baseline, 6 (33%) patients were stable, and 5 (28%) patients developed more severe photophobia. Regarding corneal cystine crystals, the condition was stable for 21 patients (that is, the same grade of corneal deposit was achieved before and after treatment) whereas there was an increase in the density of crystals for the remaining 11 patients.

The sponsor also provided following three case reports each based on a single subject:

- **Jones et al. (1991):** This case study was conducted in the United Kingdom. The study followed and treated a 2-year old girl with nephropathic cystinosis with topical cysteamine 0.5% (instilled hourly during waking hours) to one eye (right eye) for 3 months. In the study, clinical and photographic changes of corneal cystine crystal density were assessed. Per the study report, the patient had virtually complete clearance of crystals in the treated cornea and reduction of photophobia.

- **Gräf et al. (1992)**: This case study was conducted in Germany. The study followed and treated a 2-year old boy with nephropathic cystinosis with topical cysteamine 0.1% instilled every two hours (6 to 8 drops daily) for 26 weeks in the right eye and for 12 weeks in the left eye. Per the study report, a clearance of crystals from the cornea after 26 weeks was seen in the right eye and the same result was reached in the left eye after 12 weeks.

- **Ozdemir et al. (2019):** This case study was conducted in Germany. The study followed and treated a 36 years old female with cystinosis (initially with photophobia and visual deterioration) with cysteamine drops for times a day for a year. In the study, IVCM and anterior segment optical coherence tomography was performed during follow-up period. Per the study report, the following observations were made after a year of treatment: (i) photophobia was reduced, (ii) IVCM showed decrease in size and density of corneal crystals, and (iii) depth of corneal crystals did not change but crystal density score reduced with cysteamine treatment.

3.2.5 Efficacy Conclusion

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, as shown in Figure 5 and Figure 10, 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.

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.

3.3 Safety Evaluation

A high-level summary of the safety data is presented in this section. See the FDA medical review for a comprehensive safety evaluation

In OCT-1 study, eight subjects were enrolled in the study and all subjects received Cystadrops over a period of five years. In this study, on average, subjects received 4 instillations/eye/day up to Day 90 followed by 3 instillation/eye/day from Day 90 to Month 60.

In the CHOC study, 32 subjects were enrolled in the study and 15 subjects received Cystadrops. In this study, on average, subjects received 4 instillations/eye/day for a period of 90 days.

Table below shows an overview of the treatment emergent events (TEAEs) reported in the OCT-1 and CHOC studies:

	OCT-1		CHOC			
	CYSTADROPS (N=8)		CYSTADROPS (N=15)		CH 0.10% (N=16)	
Descriptive Statistics	Patients	Events	Patients	Events	Patients	Events
All adverse events	7 (87.5%)	73	10 (66.7%)	54	13 (81.3%)	69
All adverse events leading to temporary treatment discontinuation	0	0	1 (6.7%)	1	1 (6.3%)	1
All adverse events leading to treatment discontinuation	0	0	1 (6.7%)**	1	0	0
All deaths	0	0	0	0	0	0
All serious adverse events	6 (75.0%)	48	2 (13.3%)	2	2 (12.5%)	2
All serious drug-related adverse events*	1 (12.5%)	1	0	0	0	0

CH 0.10% = cysteamine hydrochloride 0.10% solution
* In the OCT-1 study, this category also included events where the causality was reported as "unknown."
** Patient withdrawn at Day 86.
Source: Table 2.5-5 of Applicant Clinical Overview Document (Module 2.5)

Per the sponsor, no TEAEs were reported as related to the treatment with Cystadrops in the OCT-1 study. In the CHOC study, 18 TEAEs (all eye disorders) were related to treatment. Four TEAEs (2 cases of eye irritation, 1 case of eye pain and 1 case of lacrimation increased) were reported by 2 subjects in the Cystadrops arm. Fourteen TEAEs (6 cases of eye pain, 3 cases of eye irritation, 3 cases of blurred vision and 2 cases of pruritus) were reported by one patient in the CH 0.10% arm.

No subjects died in both studies. In OCT-1 study, six patients experienced a total of 48 serious adverse events (SAEs; 46 were hospitalizations). In the CHOC study, 4 subjects (2 in Cystadrops and 2 in CH 0.10%) reported SAEs.

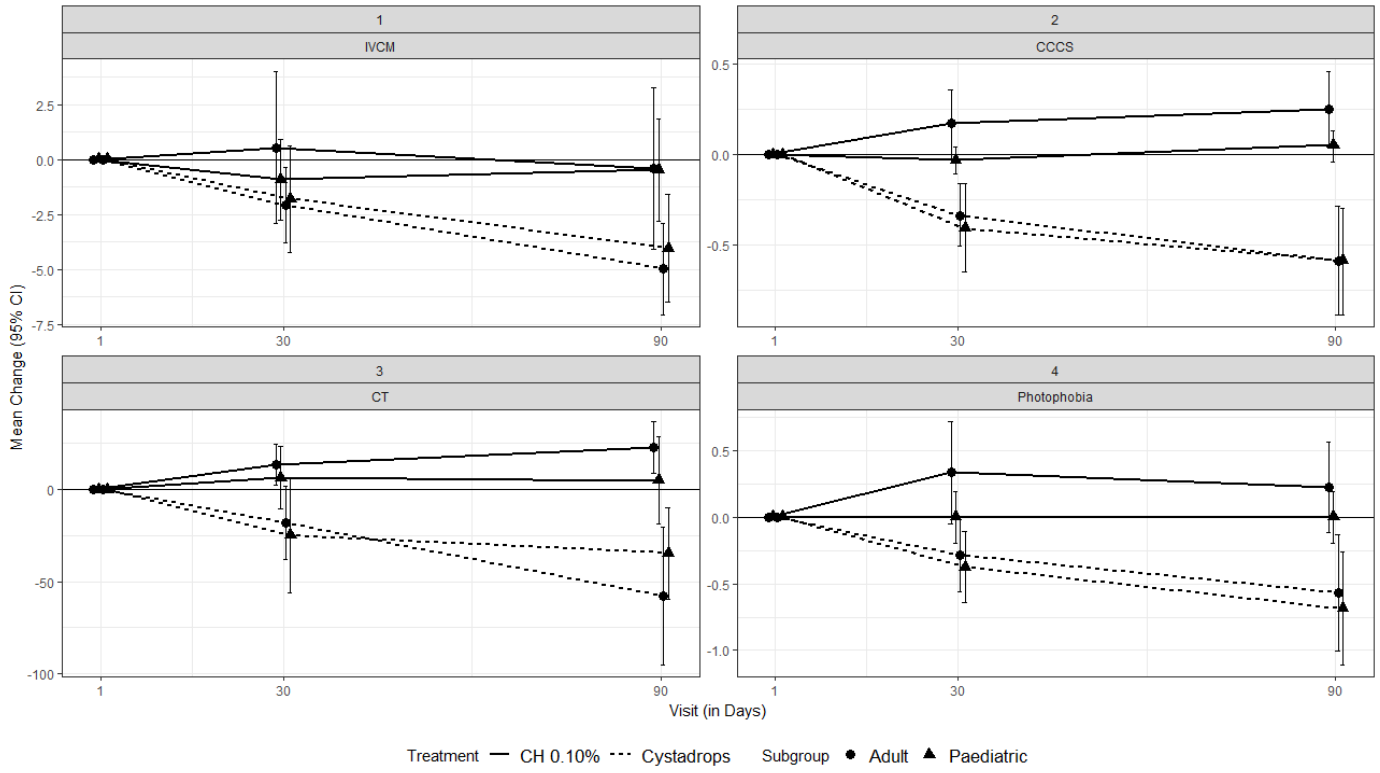
Regarding withdrawal from the study due to drug-related adverse events, no subject in OCT-1 study reported discontinuation due to adverse event. In the CHOC study, 2 subjects discontinued treatment temporarily (one each in both arms) and one subject in the Cystadrops arm discontinued permanently.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The primary efficacy variable of the change in IVCM (±95% CI) from baseline at each visit and the key secondary efficacy variables of the change in CCCS, CT, and Photophobia (±95% CI) at each visit were summarized in this section by age categories (<18 years [pediatrics] vs ≥18 [adults]). In the CHOC study, a total of 12 adults and 19 pediatrics were enrolled.

Figure 12 below shows the mean change in IVCM, CCCS, CT, and Photophobia over time by treatment and age groups. As shown below, in both age groups (adults and pediatrics), Cystadrops treated eyes (dashed lines) yielded significant reductions in IVCM, CCCS, CT, and Photophobia from baseline and the magnitude of reductions in the two age groups appear comparable except for small numerical differences. Note that, as in the overall population, the reductions in IVCM, CCCS, CT, and Photophobia over time in both age groups is significantly higher in the Cystadrops treated eyes than in the CH 0.10% treated eyes (dashed versus solid lines).

Figure 12: Change in IVCM, CCCS, CT, and Photophobia over time by Age group
(Full Analysis Set)



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues in the submission. However, the following items should be noted:

i) The NDA submission solely relied on foreign data (France population). The reviewer raised the applicability of the foreign data to the US population during the filing meeting and the medical review team confirmed the applicability of the France patient population to the US population during the meeting.

ii) The approval of Cystaran® in the US (NDA 200740) for the same indication was based on the primary efficacy variable of: *"The response rate of eyes that had a reduction of at least 1 unit in CCCS at some time point during the study when baseline CCCS ≥1, or a lack of an increase of more than 1 unit in CCCS throughout the study when baseline CCCS <1"*. Similar analysis in the current submission resulted in a 30% response rate through 3 months for Cystadrops compared to 0% for the control arm CH 0.10% in the CHOC study and 63% (5 out of 8 subjects) through year 5 for Cystadrops in the OCT-1 study. It should be noted that all subjects in the current submission had a baseline CCCS of ≥1.0.

5.2 Collective Evidence

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. 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 to 5.58; p-value < 0.001).

Also, Cystadrops treated eyes demonstrated significant reduction in the secondary efficacy variables of CCCS, crystal thickness, and photophobia compared to the CH 0.10% treated eyes. For example, as shown in Figure 5 and Figure 10, 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.

The single arm study OCT-1 also provided supporting evidence for the primary and secondary efficacy findings of 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.

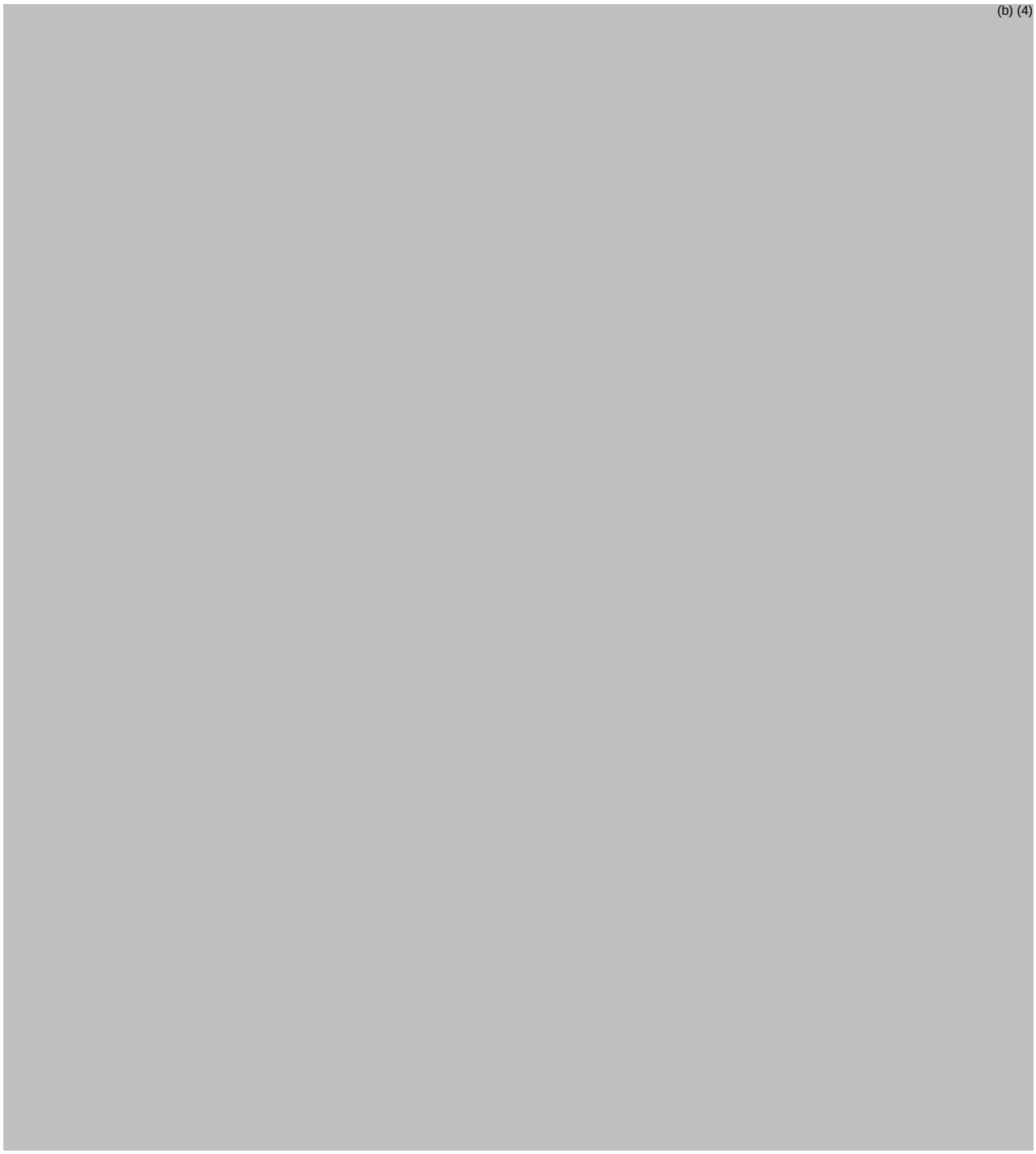
5.3 Conclusion and Recommendation

Based on the totality of evidence from the CHOC and OCT-1 studies and supporting data from the published literatures, the reviewer concludes that the application provided substantial evidence of efficacy of Cystadrops for the reduction of corneal cystine crystal density as measured by IVCM and using corneal cystine crystal score.

5.4 Labeling Recommendation

The applicant proposed the following wordings (in blue font below) in Section 14 of the draft labeling. The reviewer's comments regarding the proposed labeling are highlighted in red and green bold fonts below. Also, see a clean version of the reviewer's recommendation below.

(b) (4)



Reviewer's Recommendation:

Clinical safety and efficacy of Cystadrops were assessed in two studies: an open label, single-arm study conducted for 5 years (OCT-1) and an open-label, randomized, and controlled study conducted for 90 days (CHOC).

In the OCT-1 study, 8 patients with cystinosis (2 males and 6 females) with a mean age of 12.1 ± 4.6 (range: 7.0 – 21.0) were enrolled and received a median of 4 drops/eye/day of CYSTADROPS. In CHOC study, 32 patients with cystinosis (15 males and 17 females) with a mean age of 17.1 ± 4.6 (range: 2.9 – 62.6) were enrolled and received a median of 4 drops/eye/day. In the CHOC Study, fifteen patients were exposed to CYSTADROPS and 16 were exposed to cysteamine hydrochloride 0.10% (control arm).

Efficacy in both studies was assessed with In-Vivo Confocal Microscopy total score (IVCM score) by quantifying the cystine crystals in the 7 layers of the cornea. The IVCM total score was obtained by adding the crystal density score of the 7 corneal layers (range: 0 to 28). A decrease in IVCM total score from baseline indicated a reduction in corneal crystals.

In the OCT-1 study, the mean IVCM total score was calculated for 8 CYSTADROPS treated patients. After 30 days of treatment and at a median frequency of 4 instillations per day, an average of about 12% reduction in the IVCM total score was observed from baseline. A mean decrease in corneal cystine crystal deposits of 30%, in comparison with baseline, was maintained over time (i.e. up to month 60) with a median dosing regimen of 3 drops/eye/day (range 1 3 drops) for 7 of the 8 patients.

In the CHOC study, the mean IVCM total score was calculated for 10 CYSTADROPS treated patients. After 30 and 90 days of treatment with CYSTADROPS, 12% and 40% reduction in the total IVCM total score was observed from baseline.

In the CHOC study, CYSTADROPS demonstrated greater reduction compared to the control arm in the IVCM total score at 90 days. The average reduction in the IVCM total score at 90 days was 4.6 in the CYSTADROPS arm and 0.5 in the control arm. The treatment difference between the treatment arms (CYSTADROPS minus control) at 90 days was 3.84 (95% CI: (2.11, 5.58)).

(b) (4)

Appendix

Table 8: Summary of Total IVCM data by visit (CHOC Study)
(FAS Population)

		Cystadrops			CH 0.10%		
		Day 1	**Day 30**	**Day 90**	**Day 1**	**Day 30**	**Day 90**
Actual Total IVCM	N	20	20	20	20	18	17
	Mean (SD)	10.6 (4.18)	8.7 (2.44)	6.0 (2.08)	10.8 (3.47)	9.8 (3.72)	9.8 (3.81)
	Median	10.85	9.1	5.9	10.75	9	10
	Range	(3.2, 19.0)	(4.2, 13.4)	(2.0, 9.6)	(4.2, 16.2)	(5.2, 17.6)	(5.0, 17.7)
	95% CI	(8.7, 12.6)	(7.5, 9.8)	(5.1, 7.0)	(9.2, 12.4)	(8.0, 11.7)	(7.8, 11.8)
Change in Total IVCM	Mean (SD)	--	-2.0 (2.70)	-4.6 (3.12)	--	-0.4 (3.00)	-0.5 (3.38)
	Median	--	-1.3	-4.13	--	0.2	-1.2
	Range	--	(-7.8, 1.5)	(-11, -0.6)	--	(-7.6, 6.7)	(-7.6, 6.5)
	95% CI	--	(-3.2, -0.7)	(-6.1, -3.1)	--	(-1.9, 1.1)	(-2.2, 1.3)
Percent change in Total IVCM	Mean (SD)	--	-12.6 (20.70)	**-40.4 (16.03)**	--	-1.74 (27.32)	**-0.68 (33.05)**
	Median	--	-15.6	-43.6	--	1.71	-10.6
	Range	--	(-45.9, 31.25)	(-64.7, -8.33)	--	(-46.9, 61.47)	(-46.9, 63.07)
	95% CI	--	(-22.3, -2.88)	(-48.0, -32.9)	--	(-15.3, 11.84)	(-17.7, 16.31)

Note: Descriptive summaries are based on treating measurements of two eyes as independent

Table 9: Summary of Total IVCM data by visit (OCT-1 Study)
(FAS Population)

	Actual Total IVCM (N=16)			Change in Total IVCM (N=16)				Percent Change in Total IVCM Mean (SD)	
Visit	Mean (SD)	Median	Range	Mean (SD)	Median	Range	95% CI	All Subjects (N=16)	Subjects with median dose of 3 drops/eye/day (N=14) [a]
Day 1	11.4 (2.94)	11.0	(7.0 ,18.0)	--	--	--	--	--	
Month 1	9.9 (3.18)	10.0	(5.0 ,16.0)	-1.5 (2.45)	-2.0	(-5.0, 3.0)	(-2.8, -0.2)	-11.7 (25.09)	-13.63276
Month 3	8.2 (3.06)	8.0	(4.0 ,14.0)	-3.2 (1.80)	-4.0	(-5.0, 0.0)	(-4.1, -2.2)	-28.6 (17.49)	-31.07632
Month 6	8.6 (3.91)	7.5	(5.0 ,18.0)	-2.8 (2.29)	-3.0	(-7.0, 3.0)	(-4.0, -1.5)	-25.8 (18.63)	-30.97145
Month 9	8.1 (4.06)	6.5	(5.0 ,18.0)	-3.3 (2.41)	-4.0	(-6.0, 4.0)	(-4.5, -2.0)	-30.7 (19.78)	-36.76948
Month 12	8.1 (3.63)	7.5	(5.0 ,17.0)	-3.3 (2.08)	-3.5	(-6.0, 3.0)	(-4.4, -2.1)	-30.2 (16.87)	-35.20382
Month 18	7.9 (3.68)	7.0	(4.0 ,16.0)	-3.4 (1.79)	-3.0	(-6.0, 0.0)	(-4.4, -2.5)	-32.2 (18.10)	-35.95341
Month 24	7.9 (3.88)	7.0	(3.0 ,15.0)	-3.5 (2.07)	-3.5	(-6.0, 1.0)	(-4.6, -2.4)	-33.1 (20.83)	-37.16579
Month 30	8.7 (4.33)	8.0	(4.0 ,18.0)	-2.7 (2.68)	-3.5	(-6.0, 4.0)	(-4.1, -1.3)	-25.9 (24.31)	-31.28685
Month 36	7.5 (3.65)	6.0	(3.0 ,14.0)	-3.9 (2.31)	-5.0	(-8.0, 0.0)	(-5.1, -2.6)	-35.8 (21.57)	-39.30556
Month 42	8.3 (4.47)	6.0	(4.0 ,17.0)	-3.1 (2.77)	-3.5	(-7.0, 3.0)	(-4.5, -1.6)	-29.5 (25.37)	-34.88121
Month 48	8.2 (4.23)	5.0	(5.0 ,15.0)	-3.2 (3.04)	-4.0	(-8.0, 3.0)	(-4.8, -1.6)	-29.6 (26.97)	-31.20207
Month 60	7.9 (4.39)	5.0	(3.0 ,15.0)	-3.4 (2.78)	-3.5	(-8.0, 1.0)	(-4.9, -2.0)	-32.7 (25.40)	-36.19176

Note: Descriptive summaries are based on treating measurements of two eyes as independent
[a] One subject (SUBJID (b) (6)) with median dose of 4 drops/eye/day from Month 3 through Month 60 was excluded in this summary.

Table 10: Change in Total IVCM: Sensitivity Analysis
(Randomized Subjects)

		Cystadrops (N=30)	CH 0.10% (N=32)	Difference (95% CI) [a]
Baseline	Mean (SD)	10.3 (3.43)	10.5 (2.76)	--
	Median	9.8	9.8	
	Range	(3.2, 19.0)	(4.2, 16.2)	
Day 30	Mean (SD)	-1.7 (2.26)	-0.7 (2.37)	-1.1 (-2.2, 0.1)
	Median	-1.5	-1.1	
	Range	(-7.8, 1.5)	(-7.6, 6.7)	
Day 90	Mean (SD)	-4.2 (2.59)	-0.8 (2.60)	-3.6 (-4.9, -2.5)
	Median	-3.7	-0.8	
	Range	(-11, -0.6)	(-7.6, 6.5)	

[a] Difference and 95% CI are based on GEE model after unobserved baseline IVCM and missing IVCM data were imputed as outlined in Section 3.2.2 (RE: Handling Missing Data)

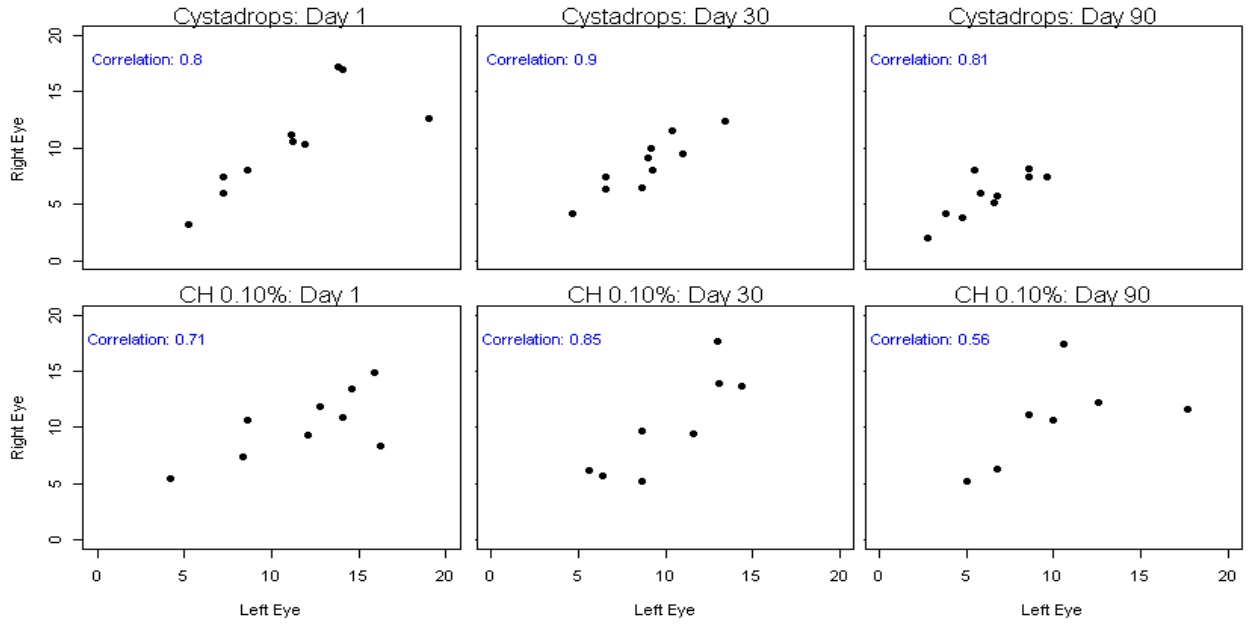
Table 11: Change in Total IVCM: Analysis based on average of two eyes
(Full Analysis Set)

		Cystadrops (N=10)	CH 0.10% (N=10)	Difference (95% CI) [a]
Baseline	Mean (SD)	10.6 (4.07)	10.6 (3.15)	--
	Median	11.0	10.7	
	Range	(4.2, 15.8)	(4.8, 15.4)	
Day 30	Mean (SD)	-2.0 (2.37)	-0.5 (2.14)	-1.3 (-3.1, 0.6)
	Median	-1.6	-0.1	
	Range	(-6.4, 0.4)	(-3.5, 2.8)	
Day 90	Mean (SD)	-4.6 (2.82)	-0.6 (1.86)	-3.8 (-5.6, -1.9)
	Median	-4.2	-1.1	
	Range	(-9.6, -0.7)	(-2.8, 2.3)	

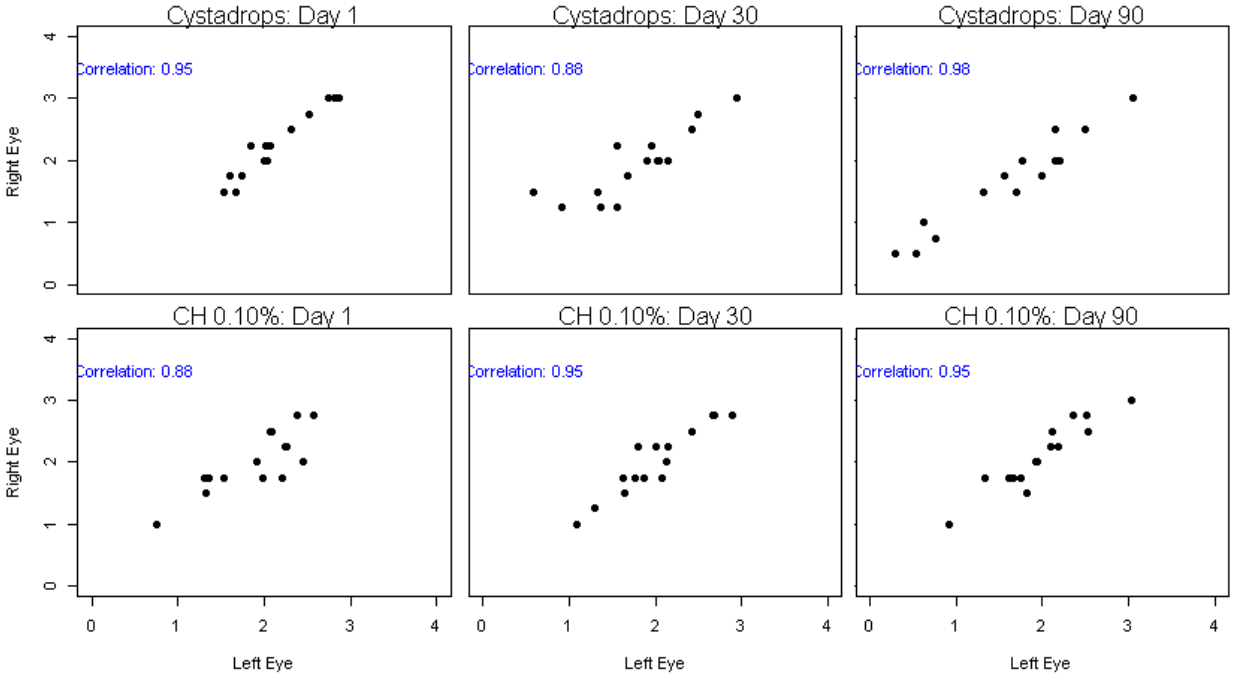
[a] Difference and 95% CI are based on ANCOVA model.

Figure 13: Scatter plot between two eyes at each visit for the primary and secondary efficacy variables (Full Analysis Set)

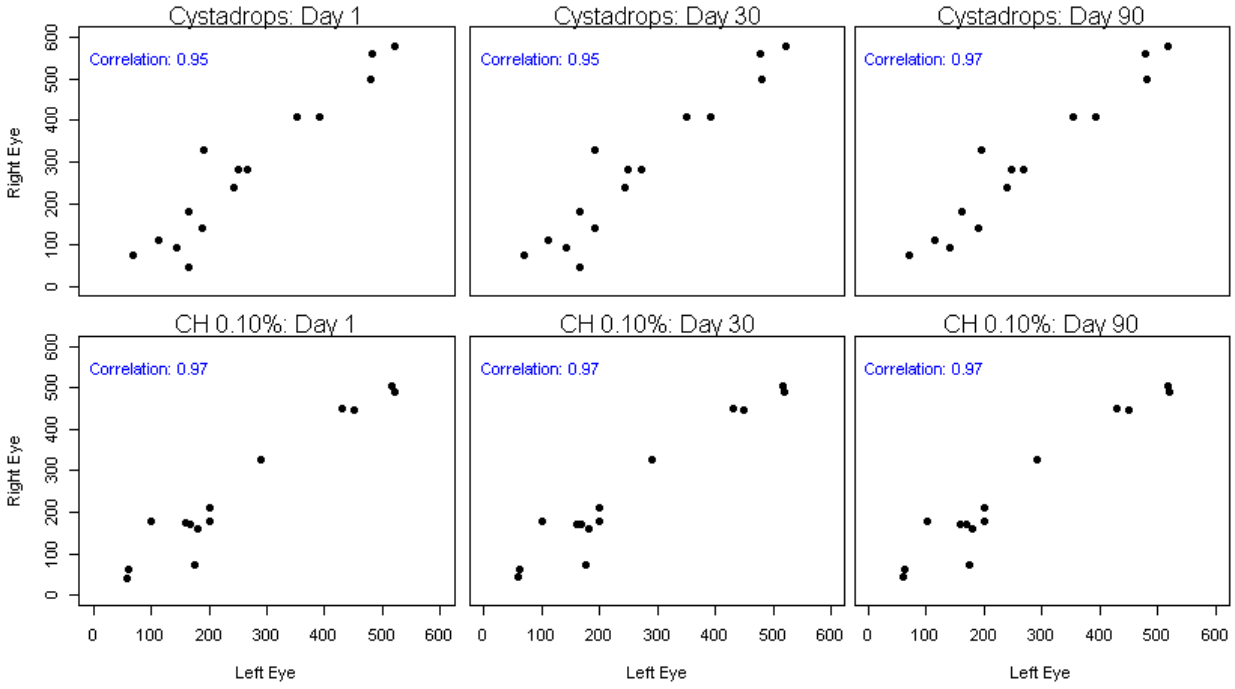
In Vivo Confocal Microscopy (IVCM)



Corneal Cystine Crystal Score (CCCS)



Crystal Thickness (CT)



Photophobia

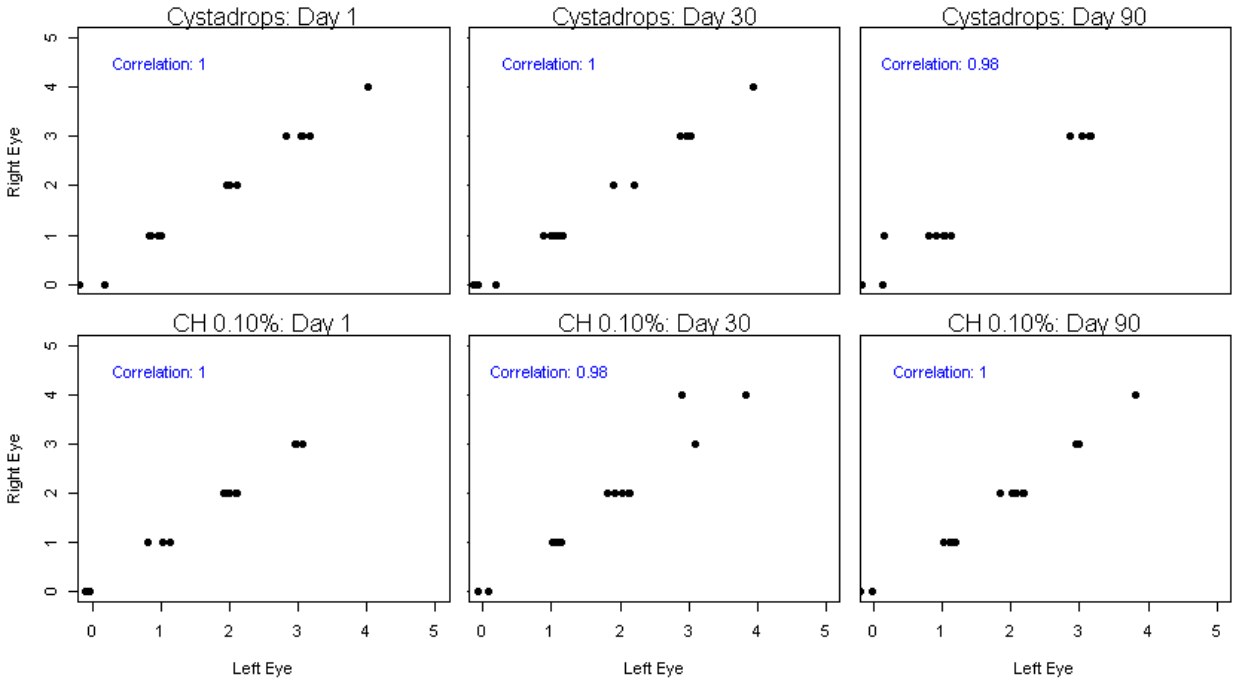


Figure 14: Change in Total IVCM by visit for each subject (CHOC Study)
(Full Analysis Set)

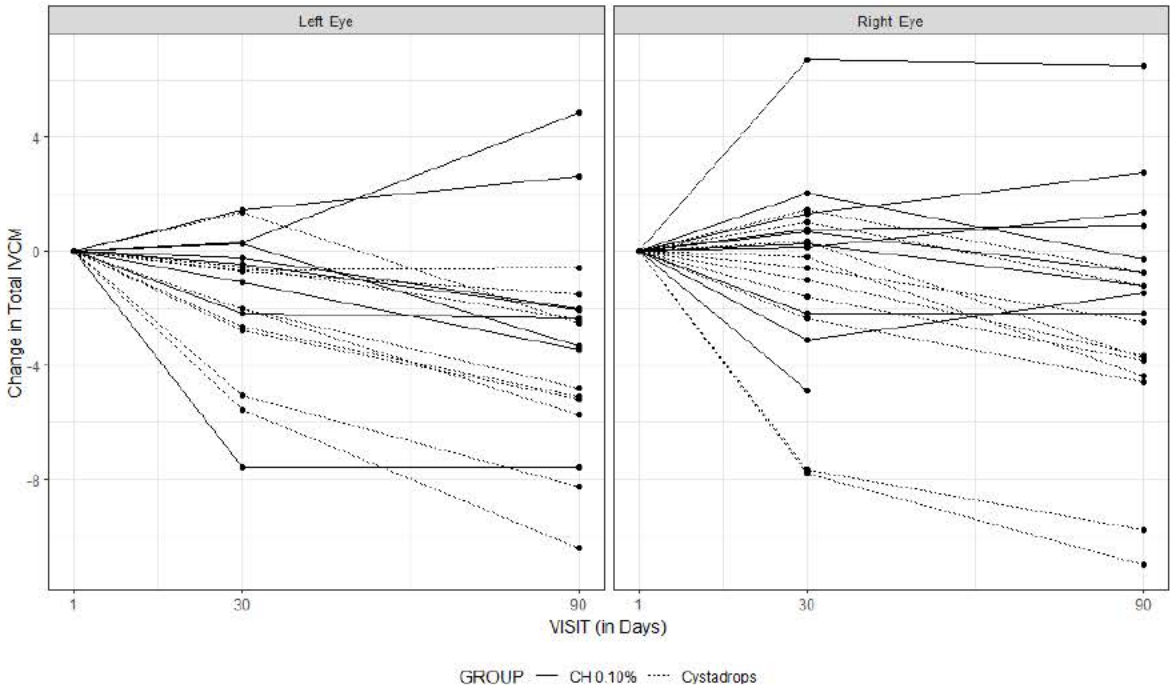
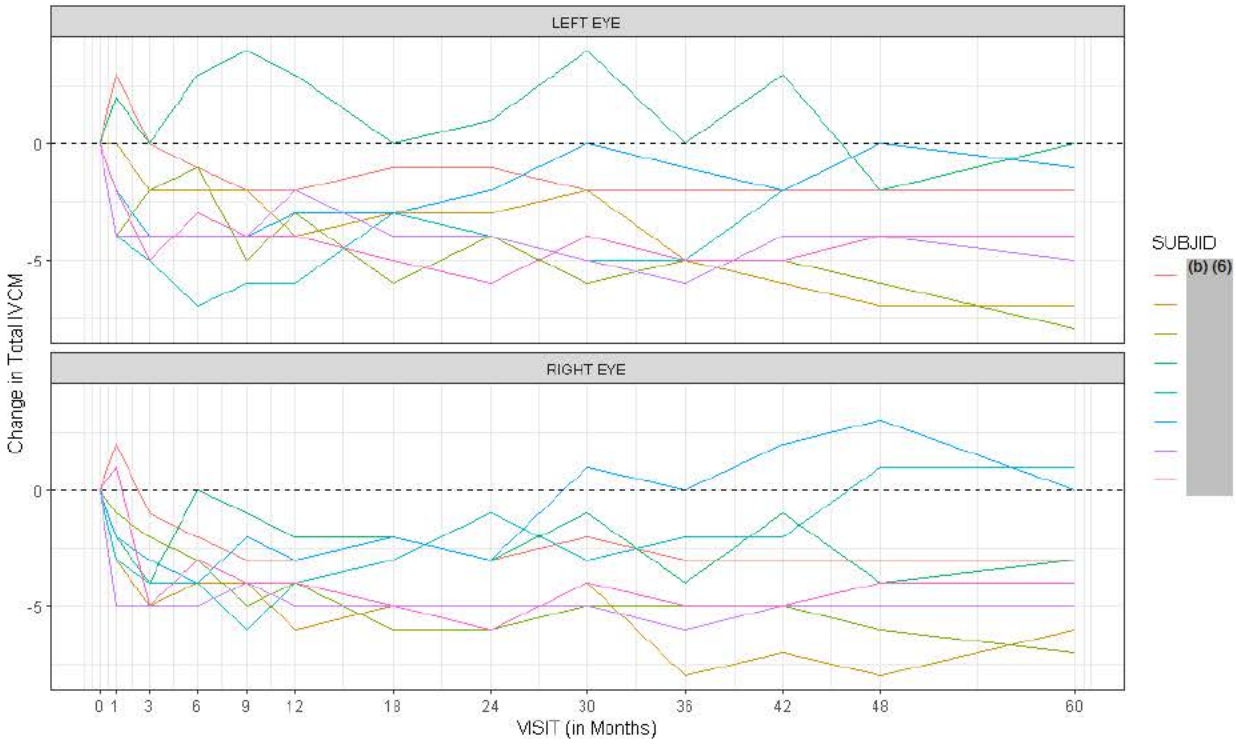


Figure 15: Change in Total IVCM by visit for each subject (OCT-1)
(Full Analysis Set)



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SOLOMON CHEFO
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I concur.