

# A New Viscous Cysteamine Eye Drops Treatment for Ophthalmic Cystinosis: An Open-Label Randomized Comparative Phase III Pivotal Study

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**PURPOSE.** The purpose of this study was to evaluate the efficacy of new viscous cysteamine hydrochloride (vCH 0.55%) compared with standard CH 0.10% drops treatment.

**METHODS.** This was an open-label, phase III, randomized, two-arm multicenter trial conducted at two centers in France. Cystinosis patients  $\geq 2$  years old were randomized 1:1 to receive eye drops, four times per day for 90 days in both eyes. We compared the superiority in reducing corneal cystine crystal density as assessed by in vivo confocal microscopy (IVCM). We also evaluated photophobia, corneal cystine crystal scores (CCCS), and cystine crystal depth measured by optical coherence tomography. Safety objectives were to assess adverse events (AEs), local adverse drug reactions, and ocular safety parameters.

**RESULTS.** We included 15 patients with vCH 0.55% and 16 patients with CH 0.10% drops for 90 days. The mean absolute change in IVCM total score at day 90 in the vCH 0.55% drops group ( $-4.6 \pm 3.1$ ) was significantly greater than and superior to the mean absolute change in the CH 0.10% drops group ( $-0.46 \pm 3.38$ ;  $P < 0.0001$ ). Photophobia, CCCS, and corneal cystine crystal depth were significantly more improved in the vCH 0.55% drops group than in the CH 0.10% group. The most frequent local adverse drug reactions in both groups were stinging, burning, redness, and blurred vision.

**CONCLUSIONS.** vCH 0.55% was effective in reducing corneal cystine crystal density and superior to treatment with CH 0.10% drops, which offer advantages over hospital pharmacy formulations and is a more preferable and convenient treatment option.

**Keywords:** cystinosis, cysteamine hydrochloride, cystine crystals, cornea, in vivo confocal microscopy, eye drops

Cystinosis is a rare autosomal recessive metabolic disorder in which cystinosis gene (*CTNS*) mutations result in defective cystine transport across the lysosomal membrane and accumulation and crystallization (disulfide-linked dimers of the amino acid cysteine) in all tissues with progressive and widespread functional impairment of kidneys, thyroid, testis, pancreas, muscle, brain, and eye.<sup>1</sup> In the eye, cystine crystal formation and accumulation in the cornea leads to photophobia, blepharospasm, corneal erosions, superficial punctate keratopathy, and band keratopathy.<sup>2</sup> Without treatment, this can result in complete loss of vision requiring keratoplasty.<sup>3,4</sup>

Although oral treatment with cysteamine reduces systemic cystine accumulation, improving prognosis, it does not prevent corneal crystal accumulation due to lack of vascularization of the cornea, whereas topical treatment with cysteamine hydrochloride (CH) drops reduces corneal crystal density and photophobia.<sup>2,5,6</sup>

Current treatment with CH drops presents significant challenges: the major obstacle is that cysteamine is unstable

at room temperature and to light exposure. In the presence of oxygen, it oxidizes to the disulphide form, cystamine, which is clinically ineffective.<sup>7</sup> Typically, standard CH drops should be applied 6 to 12 times per day, and the solution must be kept refrigerated to maintain stability. These treatment frequency and storage problems make compliance difficult. In the United States, CH drops are available in a US Food and Drug Administration (FDA)-approved 0.44% ophthalmic solution (Cystaran; Sigma-Tau Pharmaceuticals, Gaithersburg, MD, USA), and the drops should be instilled every waking hour.<sup>8</sup> In Europe, the instability of such formulations and consequent difficulties in manufacturing under specific conditions to prevent oxidation and in distribution have impeded licensure.<sup>9</sup> Thus, off-license CH solutions containing various concentrations, compositions, and buffers are prepared by hospitals or local pharmacies and are the only available option in Europe.

A new, gel-like, viscous CH formulation containing 3.8 mg/mL cysteamine (vCH 0.55%, equivalent to 0.55% CH; Cystadrops; Orphan Europe, Puteaux, France) to be instilled less



frequently than standard CH drops was developed.<sup>10</sup> The vCH 0.55% drops solution contains carmellose sodium as a viscous agent, prolonging the precorneal residence time, and can be stored at room temperature up to 7 days after opening. In the current study, treatment with vCH 0.55% drops versus treatment with the French standard CH 0.10% drops were compared for efficacy and superiority in cystinosis patients.

## MATERIALS AND METHODS

### Study Design

This was an open-label, phase III, randomized, two-arm multicenter trial conducted at two centers in Paris and Lyon, France, in 2013. Cystinosis patients  $\geq 2$  years old were randomized 1:1 to receive vCH 0.55% drops or standard CH (CH 0.10%) drops, with instillations of 1 drop per eye, four times per day, for 90 days in both eyes. The primary objective was to compare the efficacy of vCH 0.55% drops to CH 0.10% drops for superiority in reducing corneal cystine crystal density as assessed by *in vivo* confocal microscopy (IVCM) total score as described previously.<sup>9</sup> Secondary efficacy objectives were to evaluate photophobia, corneal cystine crystal scores (CCCS) by slit-lamp examination, and cystine crystal depth measured by optical coherence tomography (OCT).<sup>9</sup> Adverse events (AEs), local adverse drug reactions (LADRs), ocular safety parameters, and tolerability were assessed through the Comparison of Ophthalmic Medications for Tolerability (COM-Tol) questionnaire.

### Ethical Considerations

The study was approved by the independent ethics committee of Paris, Ile de France II and conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable European and French regulations. Written informed consent was obtained from patients  $\geq 18$  years old and from both parents of patients  $< 18$  years old before being included in the trial. The clinical trial registry number is EudraCT No. 2009-012-564-13.

### Patient Population

Included patients had a previously determined white blood cell cystine concentration  $> 1.5$  nmol half-cystine/mg protein, corneal crystal deposits as attested by a slit-lamp examination within 3 months prior to inclusion, and ability to comply with all study procedures including an eyewash regimen of four instillations per day. Patients were not included if they were less than 2 years of age or had an uncontrolled hepatic disorder, cardiovascular disease, neurologic disease, or cancer; hypersensitivity to cysteamine or any drop excipients (disodium edetate, benzalkonium chloride solution, carmellose sodium [Blanose 12M31P; Sevron Ltd, Preston, UK], citric acid monohydrate, sodium hydroxide); laboratory test results out of the normal range according to the reference laboratory values, unless they were considered clinically insignificant; or were pregnant, breast-feeding, or of child-bearing potential and not using an effective contraception method.

### Treatments

Patients were to administer one drop of vCH 0.55% drops or CH 0.10% drops in each eye four times per day at approximately 8 AM, 12 PM, 4 PM, and 8 PM. vCH 0.55% drops (3.8 mg/mL cysteamine, equivalent to 0.55% CH; Cystadrops; Orphan Europe) are from a clear, sterile, viscous

solution and are provided in a dark glass vial containing 5 mL. CH 0.10% drops (AGEPS, AP-HP Hospital Pharmacies, Paris, France) was supplied as a powder in vials and reconstituted weekly to a volume of 5 mL with 0.9% sodium chloride solution. Patients reported daily study treatment compliance in a paper-based diary.

### Efficacy Assessments

Efficacy assessments were performed at inclusion (day 1) and on days 30 and 90. IVCM score in eligible patients old enough to tolerate the procedure was evaluated as previously described.<sup>11</sup> Clinician-assessed photophobia was assessed on a scale of 0 (absence) to 5 (extreme) for each eye using a slit-lamp. CCCS was assessed by slit-lamp examination with a range from: 0.00 (for clarity at the center) to 3.00 (greatest recognizable crystal density) in 0.25 increments.<sup>2</sup> The depth of the cystine crystal deposits in the cornea was assessed by OCT and expressed in micrometers.

### Safety Assessments

LADRs (stinging, redness, burning, blurred vision, and itching) and their duration and severity were reported by patients daily on diary cards after each instillation. AEs/severe AEs (SAEs) were collected at inclusion, at center visits on days 30 and 90, and by phone on day 60. Medically important events also had to be reported and included severe redness of 50% of the conjunctival surface that did not blanch with 1:1000 topical epinephrine; persistent pain that interfered with daily activities; decrease in visual acuity from corneal damage that was greater than one line (more than five letters) on a log scale; and corneal neovascularization.

Ocular safety parameters were assessed during ophthalmologic examinations at center visits on days 1, 30, and 90. Examinations assessed visual acuity and contrast sensitivity on a logMAR scale; corneal irregularities or suspicion of keratoconus, and any degenerative changes in corneal shape by ocular topography; intraocular pressure; corneal epithelium integrity by corneal fluorescein staining and slit-lamp examination; ocular fundus; and refraction.

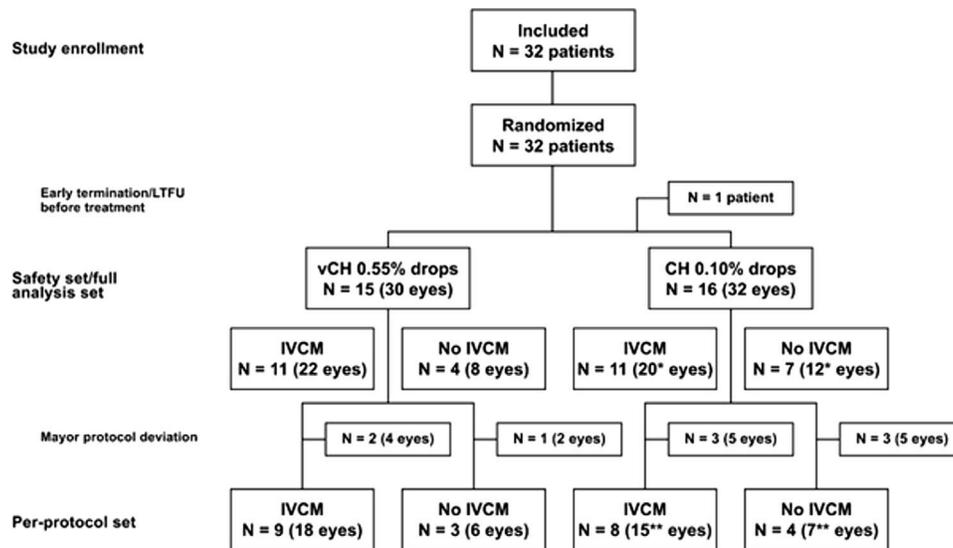
The tolerability of vCH 0.55% drops was assessed at days 30 and 90 using the COMTol questionnaire to capture topical therapy common side effects frequency.<sup>12</sup> The questionnaire, provided to adult patients, also measures the extent to which side effects and any associated limitations in routine living activities interfere with health-related quality of life, medication compliance, and patient's satisfaction with the medication.

### Randomization and Blinding

Patients were randomized 1:1 to vCH 0.55% drops or CH 0.10% drops using an interactive voice/web randomization system that assigned patients according to a randomization list produced by the service provider. Patients were stratified according to IVCM status (done/not done) and age class ( $< 12$  years, 12 to  $< 18$  years, and  $\geq 18$  years/adult). Due to the different viscosities of the study treatments, the study was open label. However, IVCM images were evaluated and scored by an independent reader who was blinded to the treatments.

### Statistical Analysis

A minimum sample size calculation was made based on the mean IVCM total score reduction results observed after 3 months of treatment from the previous pilot study.<sup>10</sup> Mean change in IVCM total score was assumed to be 0 with CH



**FIGURE 1.** Patient disposition. Patients included in the study at two centers in France (Paris and Lyon) were randomized 1:1 to vCH 0.55% drops or CH 0.10% drops. Randomization was by patient but analysis was by individual eyes. One patient was lost to follow-up after randomization and not treated. All treated patients were included in the safety and full analysis sets. Patients were stratified by IVCN capability, and only eyes for which IVCN was performed at baseline were included in the analysis for the primary efficacy end point (vCH 0.55% drops: 22 eyes; CH 0.10% drops: 20 eyes). Eight patients had major protocol deviations that excluded them from the per-protocol set (vCH 0.55% drops:  $N = 12$  [24 eyes]; CH 0.10% drops:  $N = 21$  [22 eyes]). IVCN could only be performed in one eye for two patients in the CH 0.10% drops SS/FAS (\*) and for one patient in the CH 0.10% drops PPS (\*\*).

0.10% drops and  $-3.0 \pm 2.0$  (SD) with vCH 0.55%. With a two-sided  $\alpha$  of 0.05, power at 90%, and estimated losses to follow-up of 10% per group, the calculation yielded a minimum size of 12 patients in each treatment arm (total of 24 patients) eligible for IVCN. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA), and  $P < 0.05$  indicated a significant difference. Analyses for all quantitative and categorical variables were descriptive. Unless otherwise indicated, all results presented are for the safety set/full-analysis set (SS/FAS), which included all randomized patients/eyes who received at least one dose of the study product. The per-protocol set (PPS) included all patients/eyes in the SS/FAS who had no major protocol deviations that might affect efficacy assessment. The unit of analysis was each eye.

For the primary efficacy criterion, the IVCN total score change at day 90 from baseline was assessed using a generalized estimating equation (GEE) model. This method accounts for intereye correlation and repeated measures in the same patient and is particularly appropriate for small population sizes.

The superiority of vCH 0.55% drops over CH 0.10% drops was concluded if the lower bound of the 95% confidence interval (95% CI, determined from the GEE model) for the difference in absolute change in IVCN total score between the two treatment arms (CH 0.10% drops minus vCH 0.55% drops) at day 90 was greater than 0. For secondary efficacy criteria, at day 90, changes from baseline were analyzed using a parametric analysis of covariance.

## RESULTS

### Patient Disposition and Characteristics

Thirty-two cystinosis patients were included in the study between January 9, 2013, and June 28, 2013 (Fig. 1). After randomization, one adult patient in the CH 0.10% drops group was lost to follow-up before treatment began, leaving 15 patients treated with vCH 0.55% drops and 16 patients treated with CH 0.10% drops (the SS/FAS). All 31 treated patients

completed the study, and 23 (74.2%) completed study without a major protocol deviation (the PPS) that could have affected efficacy assessments. Sex ratios were nearly equivalent in both groups, but mean age was slightly higher in the vCH 0.55% drops group (Table 1). Eleven patients in each group underwent IVCN analysis.

### Treatment Compliance

Calculated compliance from patient diaries was  $\geq 90\%$  for 93% of the patients in the vCH 0.55% drops group (14 patients) and for 88% of the patients in the CH 0.10% group (14 patients).

**TABLE 1.** Demographics and Disease Characteristics at Baseline

Characteristic	vCH 0.55% Drops, $N = 15$	CH 0.10% Drops, $N = 16$	All, $N = 31$
Sex, $n$ (%)			
Male	7 (46.7)	8 (50.0)	15 (48.4)
Female	8 (53.3)	8 (50.0)	16 (51.6)
Age at time of inclusion, y			
Mean $\pm$ SD	19.2 $\pm$ 15.5	15.1 $\pm$ 10.3	17.1 $\pm$ 13.0
Age group, $n$ (%)			
<12 y	5 (33.3)	8 (50.0)	13 (41.9)
12- <18 y	3 (20.0)	3 (18.8)	6 (19.4)
Adult	7 (46.7)	5 (31.3)	12 (38.7)
IVCN status by age group, $n$ (%)			
No IVCN	4 (26.7)	5 (31.3)	9 (29.0)
IVCN/<12 y	2 (13.3)	4 (25.0)	6 (19.4)
IVCN/12- <18 y	2 (13.3)	2 (12.5)	4 (12.9)
IVCN/adult	7 (46.7)	5 (31.3)	12 (38.7)

Results shown are for the SS/FAS.  $N$ , number of patients in group;  $n$ , number of patients with characteristic.

TABLE 2. IVCM Total Scores and Changes Between Baseline and Day 90

Variable	<i>n</i>	vCH 0.55% Drops, <i>N</i> = 22 Eyes	<i>n</i>	CH 0.10% Drops, <i>N</i> = 20 Eyes	<i>P</i> Value
IVCM total score at baseline					
Mean ± SD	20	10.6 ± 4.2	20	10.8 ± 3.5	
Range		3.2 to 19.0		4.2 to 16.2	
IVCM total score at day 90					
Mean ± SD	20	6.0 ± 2.1	17	9.8 ± 3.8	0.001*
Range		2.0 to 9.6		5.0 to 17.7	
Absolute change in IVCM from baseline					
Mean ± SD	20	-4.6 ± 3.1	17	-0.5 ± 3.4	<0.0001†
Range		-11.0 to -0.6		-7.6 to 6.5	
Relative change in IVCM from baseline, %					
Mean ± SD	20	-40.4 ± 16.0	17	-0.7 ± 33.0	
Range		-64.7 to -8.3		-46.9 to 63.1	

Results shown are for the SS/FAS. *N*, number of eyes eligible for IVCM; *n*, number of eyes analyzed.

\* Student's *t*-test reflecting the difference in the absolute IVCM scores between the two groups at day 90.

† General estimating equations model.

### Treatment Efficacy

Mean IVCM total scores (±SD) decreased during the study from 10.6 ± 4.2 at baseline to 6.0 ± 2.1 at day 90 (*P* = 0.001) in the vCH 0.55% drops group and from 10.8 ± 3.5 at baseline to 9.8 ± 3.8 in the CH 0.10% group (Table 2; Fig. 2A). Compared with IVCM images at day 1 (Fig. 2B), a decrease of crystals was clearly found in the group of CH 0.55% at 30 (Fig. 2C) and 90 days (Fig. 2D). However, compared with day 1 (Fig. 2E), no obvious difference was found in the group of CH 0.10% at 30 (Fig. 2F) and 90 days (Fig. 2G). The day 90 score was significantly lower in the vCH 0.55% drops group than in the CH 0.10% group (*P* = 0.001). For the primary efficacy end point, the absolute change in IVCM total score at day 90 was -4.6 ± 3.1 (relative change: -40 ± 16%) in the vCH 0.55% drops group, which was significantly greater than the absolute change of -0.46 ± 3.38 (relative change: -0.7 ± 33.0%) in the CH 0.10% group (*P* < 0.0001). The difference between the absolute changes was 3.8 (95% CI, 2.1–5.6), indicating that vCH 0.55% drops were superior to CH 0.10%. These results were supported by similar findings in the PPS eye population in which vCH 0.55% drops were also superior to CH 0.10% (data not shown). IVCM scores for individual corneal layers in the vCH 0.55% drops group were markedly lower at day 90 than at baseline and, for most layers, were already lower than baseline by day 30 (Fig. 3). IVCM scores in the individual corneal layers at both time points also tended to be lower in

the vCH 0.55% drops group than in the CH 0.10% group. Clinician-assessed photophobia in the vCH 0.55% drops group decreased during the study, paralleling the decrease in IVCM total score (Fig. 4). In contrast, the photophobia score did not decrease in the CH 0.10% drops group. At day 90, the mean absolute reduction in the photophobia score was significantly greater in the vCH 0.55% drops group than in the CH 0.10% drops group (*P* = 0.0048; Table 3). These results were supported by similar findings in the PPS eye population, with no decrease in photophobia in the CH 0.10% drops group (data not shown).

Mean CCCS in the vCH 0.55% drops group also decreased in parallel with mean IVCM total score (Fig. 4). However, CCCS did not decrease in the CH 0.10% group, and at day 90, the reduction in CCCS was significantly greater in the vCH 0.55% drops group than in the CH 0.10% group (*P* = 0.0015; Table 3). Corneal crystal depth also decreased in the vCH 0.55% drops group but not in the CH 0.10% group. These results were supported by similar findings in the PPS eye population, with no decrease in either CCCS or corneal crystal depth in the CH 0.10% group (data not shown).

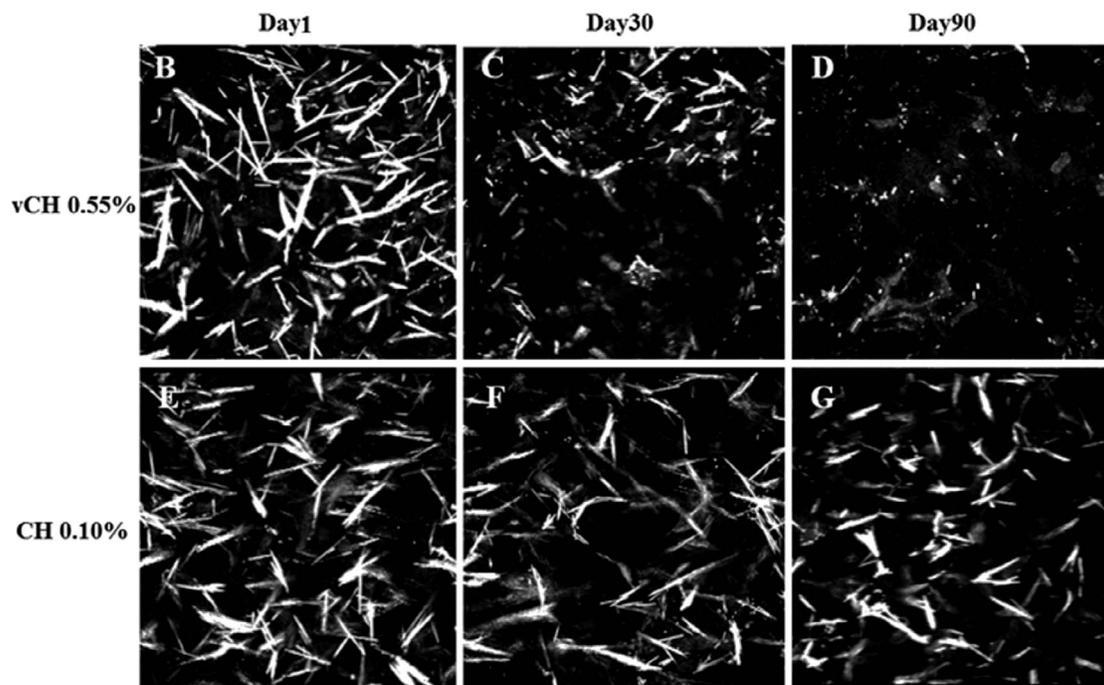
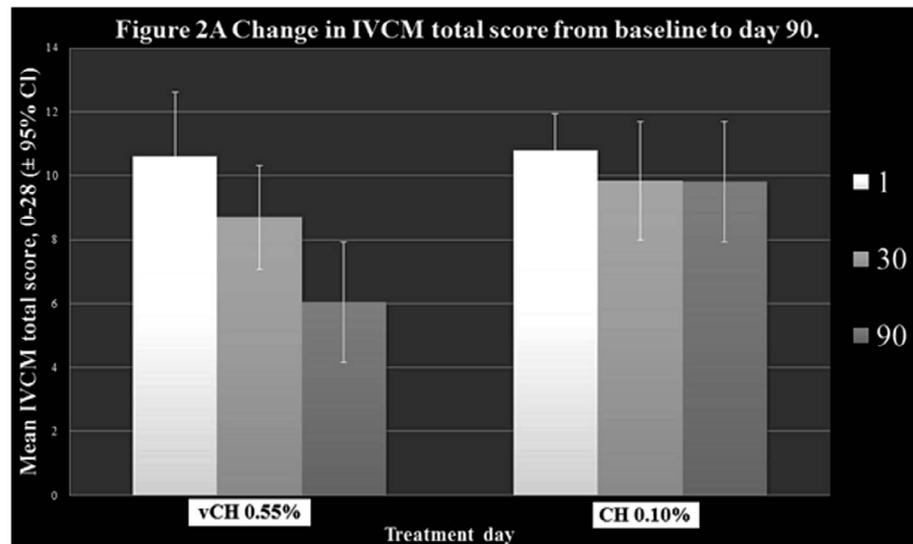
### Instillation Safety and Reactions

A total of 123 AEs were reported during the study, with 54 (43.9%) reported by 10 patients in the vCH 0.55% drops group and 69 (56.1%) reported by 13 patients in the CH 0.10% drops

TABLE 3. Baseline Values and Absolute Changes in Secondary Efficacy Measures at Day 90

Measure	<i>n</i>	vCH 0.55% Drops, <i>N</i> = 30	<i>n</i>	CH 0.10% Drops, <i>N</i> = 32	<i>P</i> Value
Photophobia, clinician-assessed, mean ± SD					
Baseline	30	1.87 ± 1.17	31	1.68 ± 1.05	
Change at day 90	30	-0.63 ± 0.77	31	0.07 ± 0.44	0.0048
Corneal cystine crystal score, mean ± SD					
Baseline		2.26 ± 0.56		1.98 ± 0.50	
Change at day 90	30	-0.59 ± 0.52	30	0.11 ± 0.24	0.0015
Corneal crystal depth by OCT, μm, mean ± SD					
Baseline	30	275 ± 159	29	260 ± 167	
Change at day 90	28	-46.3 ± 55.3	29	10.6 ± 43.6	0.0031

Results shown are for the SS/FAS. *N*, number of eyes in group; *n*, number of eyes analyzed.

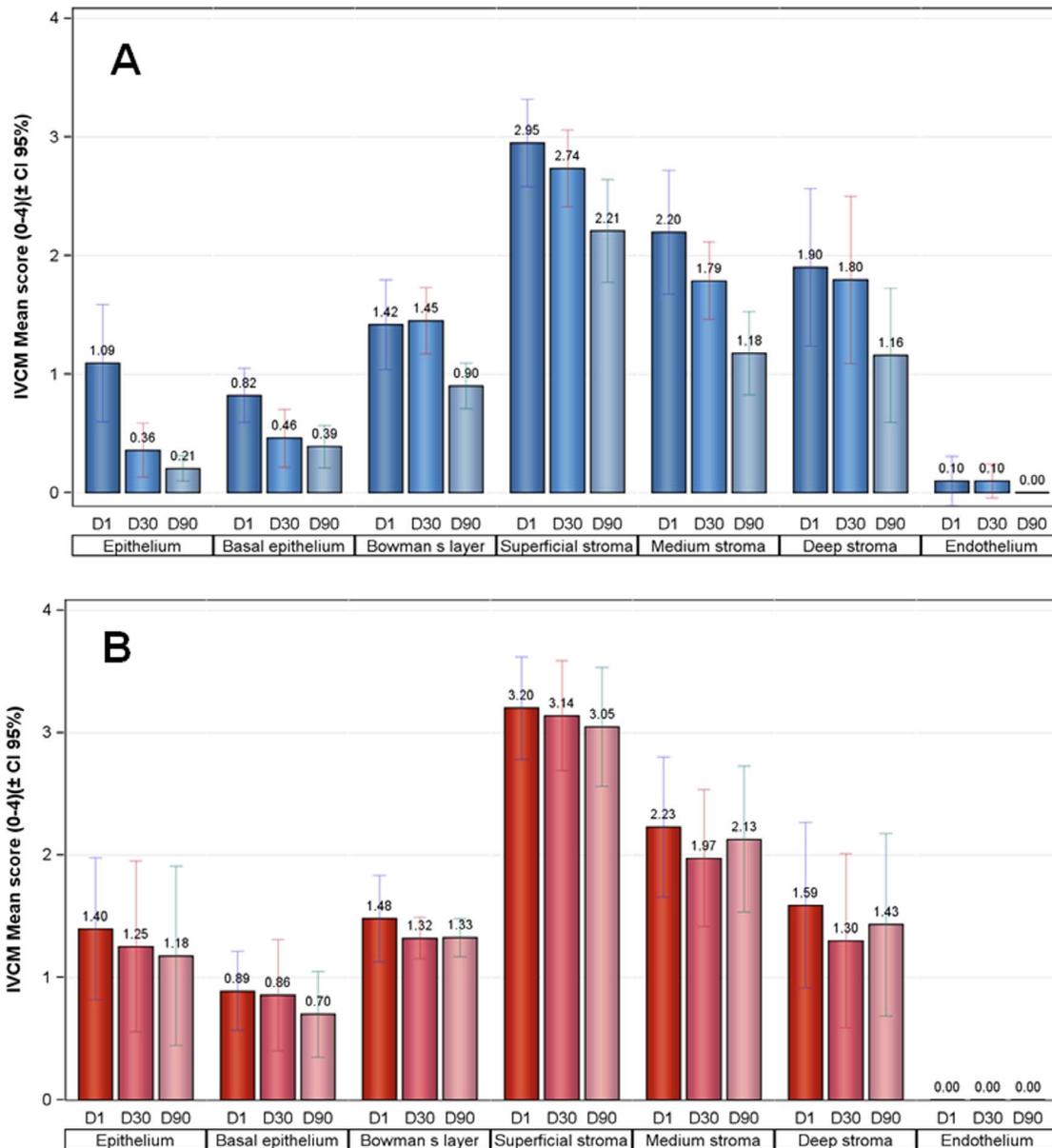


**FIGURE 2.** Change in IVCM total score from baseline to day 90. Mean IVCM total scores ( $\pm 95\%$  CIs) were similar for both groups at baseline (day 1) and lower in both groups at days 30 and 90. The IVCM total score reduction at day 90 was significantly greater in the vCH 0.55% drops group than in the CH 0.10% group. Results shown are for the SS/FAS (A). Compared with images before treatment (B), a decrease of crystals was clearly found after the instillation of CH 0.55% 30 (C) and 90 days (D) later. However, compared with the initial image (E), IVCM showed no difference for corneal crystals in the anterior cornea stroma after the instillation of CH 0.10% 30 (F) and 90 days (G) later. Images:  $400 \times 400 \mu\text{m}$ .

group (Table 4). None of the AEs were severe, and only two patients in the vCH 0.55% drops group and one patient in the CH 0.10% drops group reported treatment-related AEs. Most of the AEs were classified as eye disorders. Two patients in the vCH 0.55% drops group and one patient in the CH 0.10% drops group discontinued treatment temporarily due to AEs that were not considered related to treatment (allergic conjunctivitis and dizziness, respectively). There were four SAEs reported in the study, but none were considered to be related to treatment. There were no deaths in the study.

All 15 patients (100%) in the vCH 0.55% drops group and 11 (68.8%) patients in the CH 0.10% drops group reported LADRs (Table 4). In both groups, the most frequently reported LADR

at instillation was stinging. Burning, redness, and blurred vision were also reported by approximately 60% to 67% of the patients in the vCH 0.55% drops group and by 25% to 44% of the patients in the CH 0.10% drops treatment arm. "Other" LADRs were mainly sticky eyes and sticky eyelashes reported by patients in the vCH 0.55% drops group, which were likely due to the viscosity of the product. Overall, 83.4% of the LADRs were mild or moderate in intensity, 16.2% were severe, and 0.3% were insufferable. More than 98% of the LADRs at instillation lasted less than 1 hour. Of those lasting more than 1 hour, 42.5% were redness and 22.5% were blurred vision. None of the LADRs resulted in discontinuation of treatment.



**FIGURE 3.** IVCN scores by corneal layer. Mean IVCN scores ( $\pm 95\%$  CIs) for individual corneal layers at days 1, 30, and 90 are shown for the vCH 0.55% drops group (A) and CH 0.10% drops group (B). IVCN scores were highest in the stromal layers, which constitute 90% of the corneal thickness. Results shown are for the SS/FAS.

**Ocular Safety Parameters**

Evaluation of ocular safety parameters revealed no safety issues in either group (Table 5). However, improvements in visual acuity, visual contrast sensitivity, and corneal staining tended to be greater in the vCH 0.55% drops group than in the CH 0.10% drops group. There were no medically significant changes to intraocular pressure, eye fundus, corneal irregularities assessed by corneal topography, or refraction.

**Tolerability Questionnaire**

We asked just the adult patients in the vCH 0.55% drops group to use the COMToI, and five patients completed the COMToI questionnaire at baseline and at days 30 and 90, so the results must be interpreted with caution. At baseline, scores for all questionnaire items were generally low, indicating that most

patients were satisfied with their existing CH treatment. Overall, two patients were very satisfied, two patients were somewhat satisfied, and one patient was very dissatisfied with their treatment prior to the study. At day 90, two patients were very satisfied and three patients were somewhat satisfied with vCH 0.55% drops treatment. At day 90, all five patients indicated a preference for vCH 0.55% drops over their previous CH treatment.

**DISCUSSION**

This study demonstrated that vCH 0.55% drops are effective at reducing corneal crystal density determined by IVCN, photophobia, CCCS, and corneal crystal depth in cystinosis patients. After 90 days of four instillations per day treatment, corneal crystal density assessed by IVCN decreased by 40% in the vCH

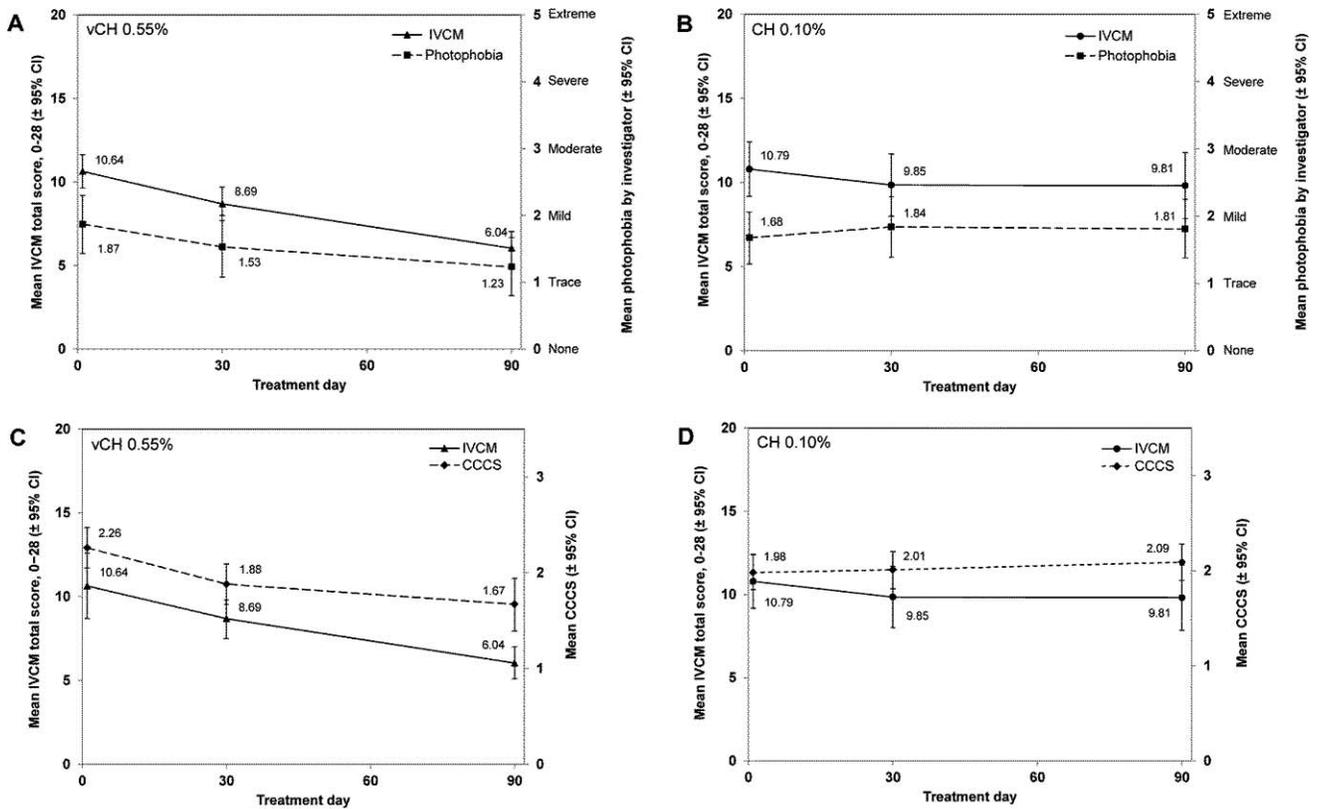


FIGURE 4. Improvements in photophobia and CCCS accompanied reductions in IVCN total score. Improvements in clinician-assessed photophobia, CCCS, and IVCN followed similar trends during the study. Photophobia and CCCS scores relative to baseline were lower at days 30 and 90 in the vCH 0.55% drops group but not in the CH 0.10% group. Improvements at day 90 were significantly greater in the vCH 0.55% drops group than in the CH 0.10% group. Results shown are for the SS/FAS.

0.55% drops group, with a decrease already evident after 30 days. The higher concentration and viscosity of the gel-like vCH 0.55% drops preparation, which increases the cornea contact time and allows the cysteamine to penetrate more

TABLE 4. Adverse Events and Local Reactions at Instillation

Type of Event	vCH 0.55% Drops, CH 0.10% Drops, Patients, N = 15	Patients, N = 16
Adverse events, n (%)		
All AEs	10 (66.7)	13 (81.3)
Severe AEs	0	0
Treatment-related AEs	2 (13.3)	1 (6.3)
SAEs	2 (13.3)	2 (12.5)
Treatment-related SAEs	0	0
Deaths	0	0
Adverse events by system organ class in at least three patients, n (%)		
Eye disorders	5 (33.3)	11 (68.8)
Infections and infestations	5 (33.3)	6 (37.5)
Local adverse drug reactions, n (%)		
Any	15 (100.0)	11 (68.8)
Stinging	12 (80.0)	8 (50.0)
Redness	9 (60.0)	7 (43.8)
Burning	10 (66.7)	4 (25.0)
Blurred vision	9 (60.0)	4 (25.0)
Itching	6 (40.0)	4 (25.0)
Other	3 (20.0)	3 (18.8)

Results shown are for the SS/FAS. N, number of patients in group; n, number of patients that experienced an event.

deeply and reach the interior layers of the cornea, likely contributed to the superior efficacy of vCH 0.55% drops.<sup>13</sup> Furthermore, the IVCN technology also showed that crystal density decreased in all corneal layers with vCH 0.55% treatment. On January 19, 2017, vCH 0.55% drops have been granted European Marketing Authorization. For instance, the United States-approved 0.44% solution is not available in Europe. In the future, it could be interesting to compare the two formulations having close concentrations for decreasing corneal crystals.

Consequent to the greater reduction in crystal density with vCH 0.55% drops, photophobia significantly improved in the vCH 0.55% drops group but not in the CH 0.10% drops group. Further, photophobia improvement paralleled the decrease in IVCN total score, with measurable improvement evident by day 30. The reduction in photophobia symptom intensity was a consequence of reduced crystal density and represents a clinical benefit for cystinosis patients, improving their quality of life.

Moreover, visual acuity and visual contrast sensitivity improved to a greater extent with vCH 0.55% drops than with CH 0.10% drops. vCH 0.55% drops also reduced the corneal staining score, reflecting improvement in corneal health, preventing deterioration, and avoiding or delaying surgical corneal repair or replacement.

Treatment in both arms caused some brief discomfort following instillation, the most common was stinging or burning; the majority of these reactions were of mild or moderate intensity. Such discomfort is common with all CH solutions because an acidic pH is necessary to maintain CH stability, and they contain the preservative benzalkonium

TABLE 5. Ocular Safety Evaluation Results at Baseline, Day 30, and Day 90

Measure	<i>n</i>	vCH 0.55% Drops, <i>N</i> = 30	<i>n</i>	CH 0.10% Drops, <i>N</i> = 32
Visual acuity logMAR scale, mean ± SD				
Baseline	22	0.24 ± 0.36	29	0.16 ± 0.30
Absolute change at day 30	22	−0.06 ± 0.11	29	−0.02 ± 0.10
Absolute change at day 90	22	−0.10 ± 0.15	29	−0.07 ± 0.15
Visual contrast sensitivity scale, mean ± SD				
Baseline	22	0.57 ± 0.37	29	0.44 ± 0.31
Absolute change at day 30	22	−0.13 ± 0.17	26	−0.03 ± 0.14
Absolute change at day 90	22	−0.20 ± 0.27	27	−0.14 ± 0.20
Corneal staining total score, mean ± SD				
Baseline	30	2.1 ± 4.4	31	0.9 ± 2.6
Absolute change at day 30	30	−1.6 ± 3.5	31	0.2 ± 0.8
Absolute change at day 90	30	−1.5 ± 3.2	31	−0.6 ± 2.5
Intraocular pressure (mm Hg), mean ± SD				
Baseline	28	15.6 ± 4.2	23	15.1 ± 2.9
Day 30	28	15.8 ± 3.2	24	14.8 ± 2.5
Day 90	27	15.0 ± 3.2	24	13.0 ± 3.0

Results shown are for the SS/FAS. *N*, number of eyes in group; *n*, number of eyes analyzed.

chloride, a known irritant. Stinging and burning reactions were more common with vCH 0.55% drops, which may be due to the fivefold higher concentration of CH in vCH 0.55% drops and to the longer corneal residence time of the viscous solution. Some vision blurring accompanied the instillation of the gel-like vCH 0.55% drops, which was to be expected given the viscosity of the solution. These AEs were manageable: no patients in either group discontinued treatment due to local reactions.

The power of the study was based on the high sensitivity of IVCM, which enables precise evaluation of corneal crystal deposits,<sup>11</sup> but it was also sufficient to detect significant differences in crystal density determined by CCCS, crystal depth determined by OCT, and in clinician-assessed photophobia in a limited number of patients.<sup>14</sup> This is an important consideration, given the rarity of cystinosis and the difficulty of recruiting large numbers of these patients in clinical trials. In this clinical study, vCH 0.55% drops were not compared to an equivalent concentration of CH (0.55%) because such a solution was not commercialized anywhere at the time of the study. Other CH formulations available in Europe at the time of the study corresponded to heterogeneous preparations, prepared mainly at hospital pharmacies, which differ in terms of active concentration, excipients, or buffers and did not permit any relevant comparison. Even with the high sensitivity of IVCM, there were still some patients who could not tolerate this corneal contact examination. Nine patients were not examined for the IVCM due to difficulties in complying with the study procedure: the choice was to include patients as young as 2 years old even if it was obvious that they would have difficulties complying with IVCM requirements, such as staying immobile for a few minutes. Nine patients without a IVCM evaluation were a mean age of 7 years (minimum to maximum, 2–12 years), and 23 patients with a IVCM evaluation had a mean age of 21 years (minimum to maximum: 5–62 years).

The efficacy of vCH 0.55% drops in reducing corneal crystal density was demonstrated to be superior to CH 0.10% drops. In addition, the gel-like preparation may be a more preferable, convenient, and effective treatment option. The fewer instillations and storage convenience of vCH 0.55% drops are attractive features that are likely to improve treatment compliance and simplify treatment for cystinosis patients faced

with a lifetime of daily instillations. vCH 0.55% drops significantly reduced photophobia as well, providing patients with measurable relief of one of the principal symptoms of cystinosis. vCH 0.55% drops also appeared to reduce the evidence of corneal complications, and because preventing corneal deterioration is one of the primary goals of treatment, vCH 0.55% drops may delay or prevent the need for corneal repair or replacement.

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