Sponsor:	**Orphan Europe, SARL**
Study title:	**Cysteamine Hydrochloride for nephrOpathic Cystinosis, open-label Phase III pivotal study**
EudraCT No:	**2009-012-564-13**

Summary – Conclusions

Demographics

A total of 32 patients were included and randomised; 15 patients were randomised to the Cystadrops® treatment arm and 17 were randomised to the cysteamine hydrochloride 0.10% treatment arm. A total of 23 patients underwent IVCM prior to randomisation and 9 patients did not.

A total of 31 patients were included in the SS/FAS, 15 (48.4%) of whom were male. The mean age at inclusion was 17.1 years (range: 2.87 - 62.6 years); 19 patients were below 18 years of age. Differences in the demographic characteristics age and gender between the two treatment arms were not statistically significant.

The mean duration of the disease i.e. the time since diagnosis of cystinosis up to inclusion was 14.8±10.8 years with the mean age at diagnosis 26.6 ± 62.6months. All patients were diagnosed with infantile nephropathic cystinosis before the age of 5 years except for 1 patient in the Cystadrops® arm who was diagnosed with the late-onset form at 30 years of age. Topical cysteamine treatment (*i.e.* eye drops) had been used by all patients prior to randomisation, with 28 out of 31 patients having used topical cysteamine treatment for more than 1 year. The mean duration of topical treatment was overall 144 months, and was similar in the 2 treatment arms. Systemic treatment with cysteamine had been used by 29/31 patients for a mean duration of 119 months (range 0.394 to 414 months). There were no clinically relevant differences between treatment groups with respect to medical history or use of previous treatment.

Treatment duration and compliance

The theoretical duration of treatment was between 86 and 94 days, with a dose regimen of 4 drops per day for a theoretical total of 344 to 376 instillations. The actual mean duration of treatment intake was 89.6 ± 14.5 days, and the mean number of days on treatment was 85.5±14.5. Treatment duration and number of days on treatment were similar in the two treatment arms. The mean number of administered instillations was 316 ± 83.9 in the Cystadrops® arm and 370 ± 89.5 in the cysteamine hydrochloride (CH) 0.10% arm.

Efficacy results

Primary efficacy endpoint

The mean change in IVCM total score from baseline at Day 90 in the SS/FAS eye population was the primary efficacy endpoint in this study and included 37 eyes from 20 evaluable patients (10 in the Cystadrops® and 10 in the cysteamine hydrochloride 0.10% arm).

Synopsis Table 1 - Primary efficacy criterion: IVCM total score change from baseline at Day 90 – SS/FAS eye population with IVCM test done at baseline

	Cystadrops	CH 0.10%	P-value (GEE model)
N[a]	20	17	
Mean ± SD	-4.60 ± 3.12	-0.455 ± 3.38	<0.0001
Min ; Max	-11.0 ; -0.600	-7.60 ; 6.50	
Med. (Q1 ; Q3)	-4.13 (-5.47 ; -2.45)	-1.20 (-2.20 ; 1.35)	

As shown in Synopsis Table 1, the mean change (± SD) in IVCM total score was -4.60 ± 3.12 in the Cystadrops® arm and -0.455 ± 3.38 in the cysteamine hydrochloride 0.10% arm. The difference between the 2 treatment arms was statistically significant (p<0.0001 using a GEE model).

Using a GEE model, the difference in absolute change in IVCM total score between the 2 treatment arms (control minus Cystadrops®) at Day 90 was estimated to be 3.8435 (± 0.8853). The 95% CI of the difference was 2.1083 - 5.5786; the lower bound was above the null value and the superiority of Cystadrops® with respect to cysteamine hydrochloride 0.10% can thus be concluded.

Relative change in IVCM total score at Day 90 was also estimated. The mean IVCM total score decreased from baseline to Day 90 by 40% in the Cystadrops® arm and by 0.7% in the cysteamine hydrochloride 0.10% arm.

The difference between treatment arms was the largest at Day 90. A trend towards a lower IVCM total score in the Cystadrops® arm was already evident at Day 30.

Secondary efficacy endpoints

Synopsis Table 2 provides the results of the analyses of the secondary efficacy endpoints. A decrease from baseline in CCCS by slit lamp and in crystal thickness as determined by OCT was observed at Day 90. A decrease in photophobia (as assessed by the investigator or by the patient) was also observed at Day 90. Changes in photophobia paralleled changes in crystal density as determined by IVCM. The difference between the two treatment arms could be shown to be statistically significant <0.05 by ANCOVA) for investigator-assessed photophobia, CCCS and crystal thickness.

Synopsis Table 2 - Secondary efficacy criterion - Change from baseline- SS/FAS eye population (N= 62)

Descriptive Statistics	Cystadrops	CH 0.10%	P-value (ANCOVA)
Photophobia rated by the investigator			
N (Nmiss)	30 (0)	31 (1)	
Mean ± SD	-0.633 ± 0.765	0.065 ± 0.442	0.0048
Min ; Max	-2.00 ; 0.000	-1.00 ; 1.00	
Med. (Q1 ; Q3)	0.000 (-1.00 ; 0.000)	0.000 (0.000 ; 0.000)	
Photophobia rated by the patient			
N (Nmiss)	30 (0)	31 (1)	
Mean ± SD	-0.267 ± 0.583	0.226 ± 0.717	na
Min ; Max	-2.00 ; 0.000	-1.00 ; 2.00	
Med. (Q1 ; Q3)	0.000 (0.000 ; 0.000)	0.000 (0.000 ; 1.00)	
CCCS			
N (Nmiss)	30 (0)	31 (1)	
Mean ± SD	-0.592 ± 0.523	0.105 ± 0.240	0.0015
Min ; Max	-1.75 ; 0.000	-0.250 ; 0.500	
Med. (Q1 ; Q3)	-0.500 (-1.00 ; 0.000)	0.000 (0.000 ; 0.250)	
Crystal thickness by OCT (µm)			
N (Nmiss)	28 (2)	29 (3)	
Mean ± SD	-46.3 ± 55.3	10.6 ± 43.6	0.0031
Min ; Max	-230 ; 84.0	-95.0 ; 83.0	
Med. (Q1 ; Q3)	-34.0 (-74.5 ; -12.5)	20.0 (-8.00 ; 42.0)	

na = not applicable: ANCOVA model did not converge

Safety results:

Ten (67%) patients in the Cystadrops® arm and 13 (81%) patients in the cysteamine hydrochloride 0.10% arm reported AEs during the study. Four patients (2 patients in each treatment arm) experienced SAEs and 1 patient (cysteamine hydrochloride 0.10% arm) experienced neovascularisation of the left eye. No deaths were reported. Only 2 patients (1 in each treatment arm) temporarily discontinued treatment due to AEs; 1 additional patient in the Cystadrops® arm discontinued at Day 86 due to allergic conjunctivitis and did not restart treatment. None of these AEs or SAEs were considered by the investigator to be related to study treatment.

The most frequently reported AEs coded to the MedDRA SOC were "Eye disorders". All 18 AEs considered as related to treatment (reported by 2 patients in the Cystadrops® arm and 1 patient in the cysteamine hydrochloride 0.10% arm) coded to this SOC.

All patients in the Cystadrops® arm and 69% of the patients in the cysteamine hydrochloride 0.10% arm reported LADRs. The most frequently reported LADR at instillation in both treatment arms was stinging, which was reported by 80% of the patients in the Cystadrops® arm and 50% of the patients in the cysteamine hydrochloride 0.10% arm. Burning, redness and blurred vision were also reported by ≥ 60% of the patients in the Cystadrops® arm. More than 98% of the LADRs were reported as lasting less than 1 hour.

Other ocular safety parameters (visual acuity, visual contrast sensitivity and corneal staining) remained stable or showed slight improvement over the treatment duration, with a trend to improvement seen more frequently in the Cystadrops® arm in comparison with the cysteamine hydrochloride 0.10% arm. No changes with respect to baseline in the aspect of the eye fundus, intraocular pressure, eye topography or eye refraction were observed over the duration of the study in either treatment arm.

The COMTol Questionnaire was only provided to adult patients in the Cystadrops® treatment arm.The results showed little change in patient satisfaction following a switch in treatment from cysteamine hydrochloride 0.10% to Cystadrops® and only a slight improvement in compliance. However, at the end of the study when patients were asked to indicate a preference, all 5 patients who responded to the questionnaire preferred Cystadrops® over cysteamine hydrochloride 0.10% for reasons linked to efficacy (4 patients) or tolerability (1 patient).

Conclusion

In conclusion, the results of this study confirm and extend to a larger patient population those obtained during the Cystadrops®-OCT-1 pilot study. They demonstrate that Cystadrops®, a viscous eye drops solution, containing 0.55% cysteamine hydrochloride and at a dosage regimen of 4 instillations/day is effective and well-tolerated in paediatric and adult patients with cystinosis presenting with corneal cystine crystal deposits.