Sponsor:	**Orphan Europe, SARL**
Study title:	**Adaptive dose regimen of Cystadrops for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis: an open label, dose-response pilot study "OCT-1"**
EudraCT No:	**2007-006024-35**

Summary – Conclusions:

Demographics

A total of 8 patients entered the study. All patients/eyes were included in the SS and FAS analysis populations. Of the 8 patients, 2 (25%) were male. The mean (SD) age at inclusion was 12.1 (4.6) years (range: 7.0 - 21.0 years). Seven patients were below 18 years of age; 4 (50.0%) were below 12 years of age and 3 (37.5%) were 12 – 17 years of age. All patients were diagnosed with infantile nephropathic cystinosis. The mean (SD) duration of the disease *i.e.* the time since diagnosis of cystinosis up to study inclusion was 10.6 (4.2) years. The age at diagnosis of nephropathic cystinosis ranged from birth to 38 months, with a mean of 17.5 months and a median of 15.5 months. Three (37.5%) patients had undergone renal transplantation prior to study inclusion, at a mean age of 10.3 years. All patients were under systemic and topical treatment with cysteamine at the time of study inclusion. Patients had received topical treatment (cysteamine hydrochloride [CH] 0.10% eye drops) for a mean period of 35.6 months (range: 2.1 – 114.7 months) prior to inclusion at a median frequency of 4 instillations per day (range: 3 to 5 instillations per day).

Treatment duration and compliance

Topical treatment with CH 0.10% was continued during the run-in period. At Day 1, treatment with Cystadrops® was initiated at the same frequency (6 patients at 4 instillations/day, 1 patient at 3 instillations/day and 1 patient at 5 instillations/day). The mean (SD) duration of treatment with Cystadrops® was 59.8 (0.21) months (range: 59.5 to 60.1 months).

Dose adaptation was allowed at each visit until Month 48. At Day 30, the number of instillations was decreased by one for 1 patient. At Day 90, the prescribed number of instillations was decreased by 1 for all patients following stabilisation of ocular findings. This latter adaptation resulted in a decrease in the median number of instillations prescribed to 3 per day up to Month 60. (Further dose adaptation was performed for individual patients at Month 24 and Month 42 which did not affect the median value). Compliance based on daily diary card recordings ranged from 97.6% to 100.2%, with all patients but one following the frequencies prescribed.

Safety results

Seven (87.5%) of the 8 patients reported 73 TEAEs during the study. Six (75%) patients experienced a total of 48 SAEs. One SAE (corneal neovascularisation) was considered after review to have a "reasonably possible" relationship to treatment with Cystadrops®. No deaths and no pre-defined serious ocular AEs were reported. Over the 5-year duration of the study, none of the patients discontinued treatment (either permanently or temporarily) due to an AE.

The most frequently reported AEs coded to the MedDRA SOC "Infections and infestations"; none of the events which coded to this SOC were considered to be related to treatment. A total of 5 TEAEs coding to the SOC "Eye disorders" were reported by 2 patients. Aside from the report of corneal neovascularisation, 2 events (chalazion and papilloedema) were reported as not related to treatment, and the relationship of the remaining 2 events (hordeolum and dry eye) was reported as unknown.

Information was provided in the patient diaries for a total of 16,282 instillations. All patients reported at least 1 LADR. The most frequently reported LADR at instillation of Cystadrops® was stinging, which was reported by 7 patients. Stinging was reported following 19% of all instillations and represented approximately 55% of all the LADRs reported up to Month 24. Stinging was also the most frequently reported LADR after instillation of CH 0.10% during the run-in period. The next most frequent events at instillation of Cystadrops® were blurred vision (reported by 6 patients) and burning (reported by 4 patients), which represented approximately 26% and 19%, respectively, of all LADRs reported. Most LADRs were reported as "mild" (49.5%) or "moderate" (47.3%) in intensity; less than 3% overall were reported as "severe" or "unbearable". All LADRs were transient, with approximately 50% having a duration of 5 seconds or less. No LADR was reported as lasting more than 3 minutes after instillation.

The VAS score for pain at instillation of Cystadrops® was higher than what was reported for CH 0.10%. However, the mean pain score tended to decrease over time after Day 30. Mean pain scores remained ≤ 20 out of a possible maximum score of 100 from Day 90 onwards.
Intraocular pressure remained within the normal range over the duration of the study. Routine laboratory assessments also remained within normal ranges for virtually all parameters.

Efficacy results

At a median frequency of 4 instillations per day, a significant decrease in IVCM total score with respect to baseline was observed after only 30 days of treatment (from a mean [SD] total score of 11.38 [2.94] at Day 1 to a mean [SD] total score of 9.88 [3.18] at Day 30; $p < 0.05$ using a GEE model). After 90 days of treatment, the mean IVCM total score had decreased by 28% with respect to baseline (total score of 8.19 [3.06]). At Day 180, the mean IVCM total score was still decreased by a further 25% with respect to baseline (total score of 8.36 [3.91]); the mean IVCM total score remained relatively constant, and significantly different from baseline, up to Month 60 (total score of 7.94 [4.39]).
To validate the results obtained by IVCM, the effectiveness of Cystadrops® in reducing corneal cystine crystals was also assessed by other techniques. Decreases from baseline in CCCS (by slit-lamp) and crystal thickness (as measured by HRT-II and by OCT) also confirmed the reduction in corneal cystine crystal deposits. Photophobia also tended to improve with time on treatment, whereas no changes to visual acuity or visual contrast sensitivity were observed.

Conclusion

The results of this study indicate that Cystadrops®, a viscous eye drops solution containing 0.55% of cysteamine hydrochloride, can significantly reduce corneal cystine crystal deposits in patients with cystinosis. Treatment with Cystadrops® was generally well-tolerated and its safety was shown to be good following long-term use.