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REVIEW/UPDATE

# Efficacy of a new water-free topical cyclosporine 0.1% solution for optimizing the ocular surface in patients with dry eye and cataract

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This is a pooled analysis from 2 phase III clinical trials investigating a water-free topical cyclosporine 0.1% for the treatment of moderate to severe dry eye. The analyses included 1162 patients: 35% with cataract, 20% with pseudophakia, and 45% without cataract. Demographics or baseline characteristics were comparable across groups except for age and vision. The cyclosporine-treated patients achieved large mean improvements from baseline by day 15: −3.7 in patients without cataract, −3.2 in patients with cataract, and −3.1 in pseudophakic patients. These improvements were statistically significantly higher compared with the respective vehicle groups. In the cataract subgroup, 59% of patients treated with cyclosporine achieved ≥3 grade improvements in corneal staining score, as early as day 15. The magnitude of the effect and early onset of action make this new cyclosporine solution a promising candidate for preoperative management of ocular surface in patients undergoing cataract surgery.

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Owing to epidemiological characteristics, the overlap between dry eye disease (DED) and cataract is high, and symptoms of dry eye are increasingly reported after cataract surgery.[1,2] Several studies found that approximately half of the patients presenting for cataract surgery had significant corneal punctate epithelial keratitis affecting the visual axis, with a large proportion of those entirely asymptomatic.[2–4] The ASCRS views corneal punctate epithelial keratitis as the single most critical sign that should be normalized before any form of vision-related surgery. A compromised corneal surface secondary to DED may also compromise preoperative biometry and refractive measurements for keratorefractive and phacorefractive surgeries and adversely affect expected visual outcomes, leading to postoperative patient dissatisfaction.[5–8] A recent review article presented a strong argument for the importance of adequately improving the ocular surface before surgery, from the perspective of both the patient and the provider.[9]

The first water-free cyclosporine 0.1% solution (development name, CyclASol; U.S. trade name, Vevye) was recently approved by the U.S. Food and Drug Administration (FDA) to treat the signs and symptoms of DED, demonstrating a fast and clinically meaningful improvement of the ocular surface in patients with DED within 4 weeks.[10–12] The two phase 3 studies demonstrated that the central region of the cornea benefitted the most, with significant improvement in the corneal fluorescein staining score, which is also important for biometry measurements.[5,13]

Perfluorobutylpentane, a new water-free excipient, dissolves cyclosporine in a clear solution, free of oils and surfactants. It is an ideal vehicle for ocular application of cyclosporine, which is normally water insoluble. Owing to the water-free nature, the product has no pH, no osmolarity, and does not require preservatives. Perfluorobutylpentane has a low surface tension, leading to immediate spreading and a significantly longer retention time on the ocular surface compared with water.[14] These characteristics lead to improved bioavailability consistent with the early onset of effect and improved tolerability.[15–17] In addition, the vehicle forms a small drop size of 10 μL, matching the volume of the conjunctival sac of the eye,

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minimizing overflow, mechanical irritation, and destabilization of the tear film. These properties of the vehicle likely contribute to the efficacy of the product.

Based on the characteristics above, the water-free cyclosporine 0.1% solution should be an ideal treatment modality to manage the ocular surface before cataract surgery. In the clinical trials investigating the efficacy and safety of the product, approximately 35% of patients with DED had concomitant cataract. Therefore, we aimed to evaluate the efficacy of cyclosporine 0.1% solution specifically in patients with coexisting cataract and DED.

## METHODS

### Study Design

This is a post hoc analysis that pooled data from ESSENCE-1 and ESSENCE-2, which were randomized, double-masked, vehicle-controlled studies with the aim to assess efficacy, safety, and tolerability of cyclosporine 0.1% solution for the treatment of signs and symptoms of DED.[11,12] ESSENCE-1 was conducted at 9 clinical sites in the United States from October 19, 2017, to May 22, 2018, and enrolled 328 patients. The ESSENCE-2 study was conducted at 27 clinical sites in the United States from November 19, 2020, to September 3, 2021, and enrolled 834 patients. Both studies were performed in accordance with the HIPAA of 1996 and the tenets of the Declaration of Helsinki. The studies complied with the International Conference on Harmonization guideline on Good Clinical Practices and all other applicable local and federal regulatory requirements and laws. The protocols were registered at www.clinicaltrials.gov (NCT03292809/NCT04523129).

After written informed consent was obtained, patients who met all eligibility requirements started with an open label, 2-week run-in period using a commercially available artificial tear substitute (Systane Balance) twice daily. On confirmation of the study eligibility criteria, patients were randomized to one of the 2 treatment arms: cyclosporine 0.1% or vehicle. ESSENCE-1 consisted of an 84-day treatment period, and ESSENCE-2 consisted of a 29-day treatment period. In both trials, the primary endpoint assessment was at day 29. During both studies, participants dosed a single drop per eye twice daily.

### Patients

Eligibility criteria were similar in both studies. Patients were enrolled if they met all of the following inclusion criteria at screening and at the time of randomization: presence of high total corneal fluorescein staining score (tCFS ≥10, using the National Eye Institute [NEI] scale [0 to 15]), high symptom score (Ocular Surface Disease Index [OSDI] ≥20 in ESSENCE-1, and eye dryness score ≥50 [0 to 100] in ESSENCE-2), a significant conjunctival lissamine green staining score (≥2 [0 to 10], using Oxford scale), and decreased tear production (unanesthetized Schirmer test score between ≥1 mm and ≤10 mm at 5 minutes). Key exclusion criteria were clinically relevant abnormal slitlamp findings including lid, conjunctiva, or corneal conditions. Patients who wore contact lenses, had a recent intraocular surgery or any ocular laser procedure (within 6 months before screening), or a history of treatment with topical cyclosporine or lifitegrast within 2 months before screening were also excluded. Patients were not allowed to take eyedrops concomitantly during the studies.

The eye with a higher tCFS score of each patient was designated as the study eye at entrance. If the 2 eyes were the same, the right eye was designated as the "study eye." Ocular symptoms were assessed per patient, not per eye.

For the pooled analysis, the results of the full analysis set population from the 2 pivotal phase 3 studies were pooled and based on the medical history of study participants stratified into 3 groups: pseudophakic patients and patients with and without concomitant cataract. The following endpoints were assessed: change from baseline in tCFS and central corneal fluorescein staining (cCFS) using the NEI scale and proportion of responders for tCFS and cCFS (≥3 and 1 grades improvement) at days 15 and 29 within overall population and subgroups.

### Statistical Methods

The pooled analysis was performed between October 26, 2022, and November 7, 2022. All analyses were based on the full analysis set population (all participants who had received at least 1 dose of investigational product) and the assigned treatment within each subgroup. Efficacy evaluations were performed with available data. Efficacy for mean change from baseline in tCFS and cCFS scores was separately analyzed using an analysis of covariance model with fixed effects for the treatment group and baseline value and site as covariates. Least square means for each treatment group and for the difference between treatment groups were presented from the model together with 2-sided *P* values and 95% CIs. The responder endpoints were analyzed using a logistic regression model. Two-sided 95% CIs and 2-sided *P* values for the odds ratio were reported from the logistic regression model.

## RESULTS

### Disposition and Baseline Characteristics of Participants

All 1162 participants from ESSENCE-1 (162 participants in the active group and 166 participants in the vehicle group) and ESSENCE-2 (423 participants in the active group and 411 participants in the vehicle group) were included in the pooled analysis (Figure 1). The percentage of patients discontinuing the studies was low and balanced between the treatment groups. Of the 1162 randomized patients, 1135 (97.7%) completed the studies. There were 516 participants without cataract (45%), 399 participants with cataract (35%), and 225 participants with pseudophakia (20%) (Table 1). Twenty-two patients with cataract in 1 eye and pseudophakia in the fellow eye were excluded from the subgroup analyses.

Demographic characteristics including age, sex, and disease duration were well-balanced between the 2 studies and treatment groups (Table 2). The mean (SD) age of the pooled population was 58.3 (15.23) years with a mean DED duration of 10.9 (10.16) years. Most of the patients were female (844 = 72.6%). Mean age increased by a decade from the subgroup of participants without cataract (47.2 years) to participants with clinically significant cataract (63.9 years) and to participants with pseudophakia (73.1 years). DED duration also increased accordingly, but group differences were not significant. Mean (SD) visual acuity declined with advancing age of the patients, with a logMAR of 0.077 (0.1637) in patients without cataract and 0.153 (0.1539) in patients with pseudophakia, suggesting that other factors may also have an impact on vision in older individuals (Table 1).

### Efficacy

After 4 weeks of treatment with cyclosporine 0.1%, a large mean (SD) improvement in tCFS score from baseline was seen in the overall population −3.9 (3.07) and in all subgroups: −4.5 (3.23) without cataract, −3.6 (3.03) with clinically significant cataract, and −3.30 (2.42) in pseudophakic patients. Patients without cataract showed the

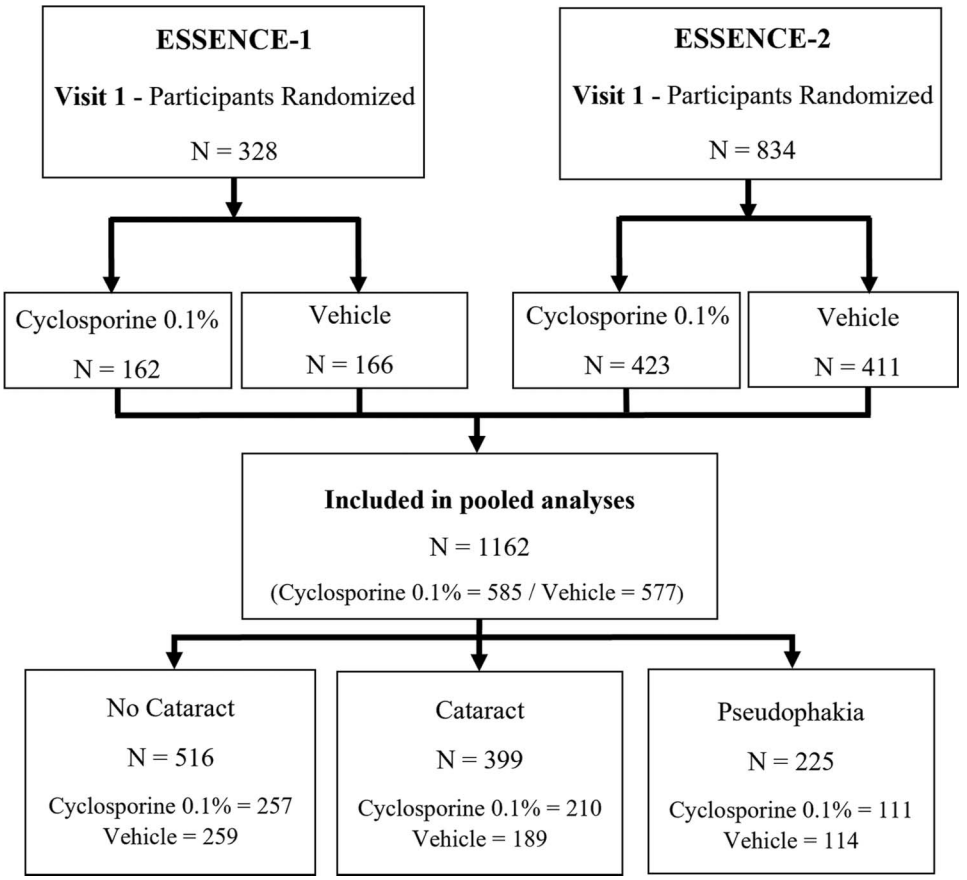


**Figure 1.** CONSORT diagram showing the flow of participants through each stage of the ESSENCE-1 and ESSENCE-2 studies and number of participants in the pool and cataract subgroups.

largest improvements from baseline, whereas patients with pseudophakia had the smallest treatment effect. The mean improvement from baseline in patients who received cyclosporine 0.1% solution was larger compared with vehicle-treated patients in the overall population and in all subgroups (overall population: $P$ = .0003; without cataract: $P$ = .0202; ongoing cataract: $P$ = .0390; pseudophakia: $P$ = .0599).

At day 15, a similar pattern was observed in mean tCFS scores. The changes from baseline in the cyclosporine 0.1%-treated patients were generally large, albeit slightly lower compared with day 29. The difference in change from baseline in tCFS was statistically significant between the cyclosporine 0.1%-treated vs vehicle arms in all subgroups (overall pooled population: −3.4, $P$ = .0003; without cataract: −3.7, $P$ = .0116; clinically significant cataract: −3.2, $P$ = .0105; pseudophakia: −3.1, $P$ = .0481) (Figure 2).

The central area of the cornea benefitted most. Mean (SD) improvements in cCFS scores from baseline after 4 weeks were seen in the overall population −0.8 (0.94) and in all subgroups: −1.0 (0.95) without cataract, −0.8 (0.92) with clinically significant cataract, and −0.6 (0.91) in pseudophakic patients. The mean improvement from baseline in patients who received cyclosporine 0.1% solution was statistically significantly larger compared with vehicle-treated patients in the overall population and in the subgroups without cataract and ongoing cataract (overall population: $P$ = .0008; without cataract: $P$ = .0278; ongoing cataract: $P$ = .0052; pseudophakia: $P$ = .8667).

In addition, clinically relevant mean (SD) improvements in cCFS scores from baseline as early as at day 15 were seen in the overall population −0.7 (0.88) and in all subgroups: −0.8 (0.94) without cataract, −0.7 (0.80) with clinically significant

**Table 1.** Baseline characteristics of pooled population ESSENCE-1 and ESSENCE-2 studies and cataract subgroups

| Baseline characteristics | Overall population | No cataract | Clinically significant cataract | Pseudophakia |
|---|---|---|---|---|
| No. of participants (%) | 1162[a] | 516 (45) | 399 (35) | 225 (20) |
| Age (y), mean (SD) | 58.3 (15.23) | 47.2 (14.10) | 63.9 (7.79) | 73.1 (7.96) |
| Female, n (%) | 844 (72.6) | 357 (69.2) | 301 (75.4) | 171 (76.0) |
| Duration of dry eye (y), mean (SD) | 10.9 (10.16) | 9.0 (8.18) | 12.5 (11.69) | 13.0 (11.89) |
| Visual acuity (logMAR), mean (SD) | 0.113 (0.1599) | 0.077 (0.1637) | 0.135 (0.1483) | 0.153 (0.1539) |

[a]Twenty-two participants with unilateral cataract were excluded from subgroup analysis

**Table 2.** Demographics and baseline tear film and ocular surface characteristics of participants enrolled in ESSENCE-1 and ESSENCE-2 studies for the treatment of dry eye with a new water-free topical cyclosporine 0.1% solution

| | ESSENCE-1 (CYS-003)[a] | | ESSENCE-2 (CYS-004)[a] | |
|---|---|---|---|---|
| Parameters assessed | Cyclosporine 0.1% (n = 162) Mean (SD) | Vehicle (n = 166) Mean (SD) | Cyclosporine 0.1% (n = 423) Mean (SD) | Vehicle (n = 411) Mean (SD) |
| Age | 61.5 (13.60) | 61.3 (12.66) | 57.6 (15.36) | 56.6 (16.30) |
| Female, n (%) | 116 (71.6) | 119 (71.7 | 306 (72.3) | 303 (73.7) |
| Total corneal fluorescein staining[b] | 11.5 (1.26) | 11.5 (1.25) | 11.5 (1.41) | 11.5 (1.36) |
| Central corneal fluorescein staining[c] | 2 (0.51) | 2 (0.52) | 2.1 (0.63) | 2.1 (0.63) |
| Total conjunctival lissamine green staining | 4.2 (1.64) | 4.4 (1.73) | 3.7 (1.72) | 3.8 (1.67) |
| Tear breakup time (s) | 2.35 (0.89) | 2.28 (0.99) | 3.36 (1.45) | 3.28 (1.56) |
| Schirmer results (mm) | 5.3 (2.82) | 5.1 (2.64) | 5.1 (2.96) | 4.8 (2.78) |
| Dryness[d] | 68.5 (21.65) | 69.86 (20.46) | 70.4 (12.53) | 70.0 (12.59) |
| Blurred vision[d] | 49.86 (29.47) | 52.21 (28.52) | 53.4 (26.56) | 51.9 (29.97) |
| OSDI[e] | 46.94 (16.73) | 47.13 (16.41) | 47.06 (21.01) | 47.15 (19.29) |
| Clinically significant cataract, n (%) | 56 (34.6) | 59 (35.5) | 161 (38.1) | 138 (33.6) |
| Pseudophakia, n (%) | 37 (22.8) | 34 (20.5) | 77 (18.2) | 84 (20.4) |

NEI = National Eye Institute; OSDI = Ocular Surface Disease Index; VAS = Visual Analog Scale
[a]See references 11 and 12 for the details of the studies
[b]Using the NEI grading scale (0-15)
[c]Using the NEI grading scale (0-3)
[d]Using VAS (0 to 100)
[e]OSDI (0 to 100)

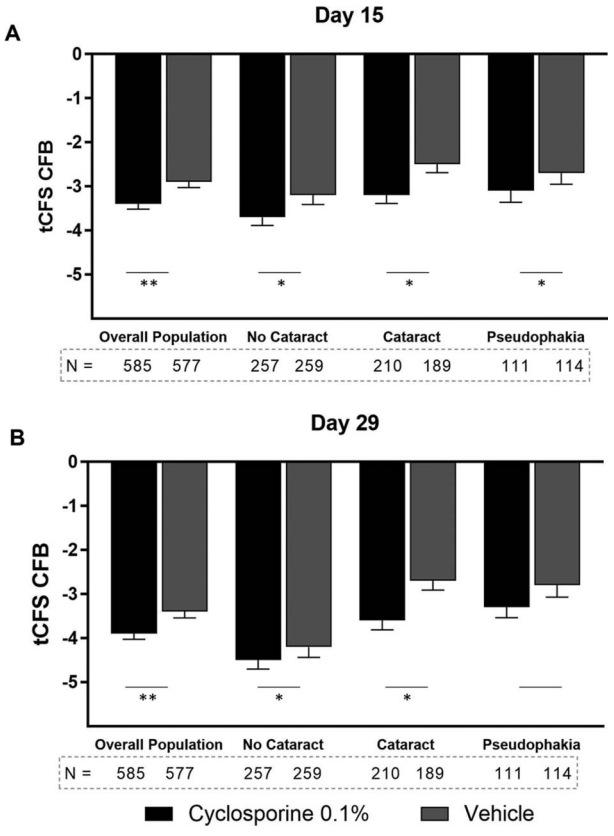


**Figure 2.** Mean CFB in tCFS score by subgroups at days 15 (*a*) and 29 (*b*) timepoints of the treatment with a new water-free topical cyclosporine 0.1% solution. *P* values from ANCOVA: **P* < .05; ***P* < .001. CFB = change from baseline; tCFS = total corneal fluorescein staining

cataract, and −0.5 (0.86) in pseudophakic patients. Again, patients without cataract showed the largest improvements from baseline, whereas patients with pseudophakia had the smallest treatment effect. The mean improvement from baseline in patients who received cyclosporine 0.1% solution was statistically significantly larger compared with vehicle-treated patients in the overall population and in the subgroups without and with ongoing cataract (overall population: $P = .0004$; without cataract: $P = .0039$; ongoing cataract: $P = .0003$; pseudophakia: $P = .6428$).

In the pooled group, 376 (66.4%) of the participants in the cyclosporine 0.1% treatment arm were tCFS responders after 4 weeks. Patients without cataract showed the highest response rates (179 = 71.3%) in the active group compared with patients with clinically significant cataract (126 = 62.4%) and pseudophakic patients (68 = 64.2%). These proportions were significantly greater compared with those in the respective vehicle groups (overall population: $P < .0001$; without cataract: $P = .0061$; clinically significant cataract: $P = .0062$; pseudophakia: $P = .0466$). At day 15, a similar pattern regarding tCFS responder rates was observed with responder rates higher than 50% in all subgroups in the treated arm (Figure 3). These rates were generally significant compared with the respective vehicle groups (overall population: $P = .0009$; without cataract: $P = .0184$; clinically significant cataract: $P = .0205$; pseudophakia: $P = .1576$).

At day 15, the proportion of cCFS responders in the pooled population was 58% (334 participants) in the cyclosporine 0.1%-treated arm: 160 (62.5%) patients without

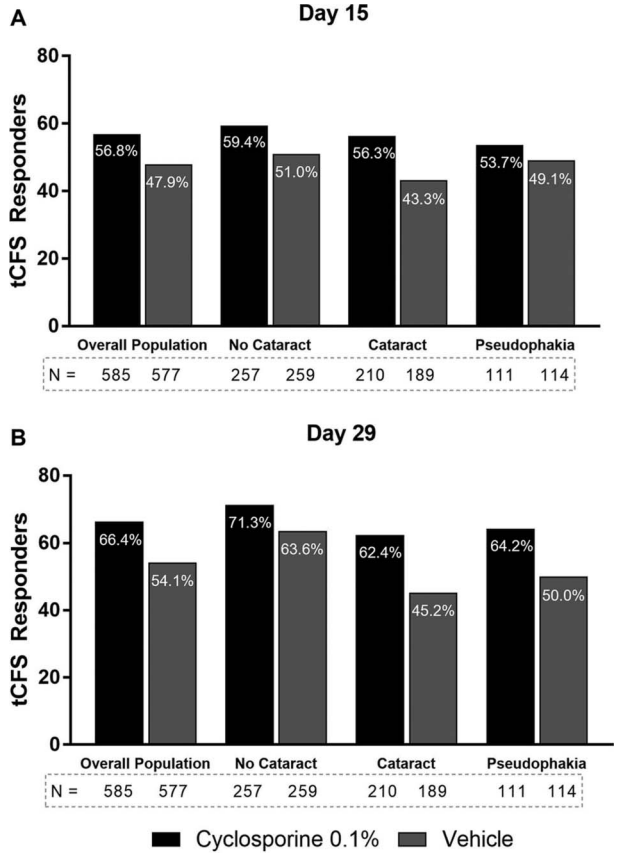


Figure 3. Proportion of participants with ≥3 severity grades improvement in tCFS (0 to 15) by subgroups at days 15 (*a*) and 29 (*b*) timepoints of the treatment with a new water-free topical cyclosporine 0.1% solution. tCFS = total corneal fluorescein staining

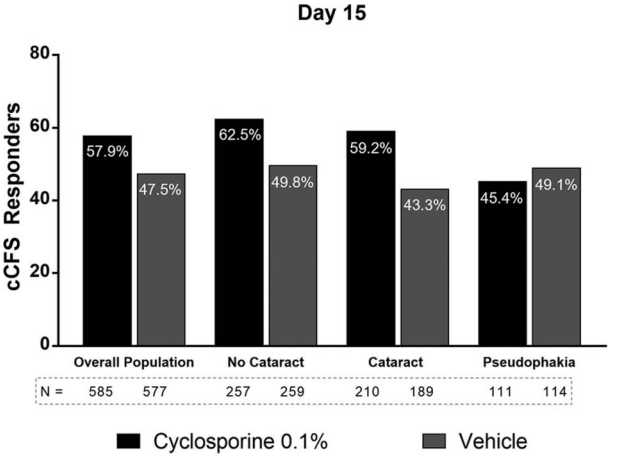


Figure 4. Proportion of participants with ≥1 severity grade improvement in cCFS (0 to 3) by subgroups at day 15 time of the treatment with a new water-free topical cyclosporine 0.1% solution. cCFS = central corneal fluorescein staining

cataract, 122 patients (59.2%) with clinically significant cataract, and 49 (45.4%) pseudophakic patients. The difference between the active and vehicle arms was significant in the overall population ($P$ = .0005) and in subgroups: without cataract ($P$ = .0047) and with cataract ($P$ = .0012) (Figure 4).

After 4 weeks of treatment, all groups showed statistically significant improvements from baseline in blurred vision and dryness scores without appreciable differences between groups and treatments. The tCFS responders, irrespective of treatment, had statistically significant improvements at day 29 for a variety of symptoms compared with nonresponders (severity of dryness: responder, −13.5; nonresponder, −8.4; $P$ = .0002; frequency of dryness: responder, −12.5; nonresponder, −8.4; $P$ = .0022; blurred vision: responder, −8.1; nonresponder, −5.4; $P$ = .0409; awareness of dry eye symptoms: responder, −12.3; nonresponder, −8.4 $P$ = .0033).

### Safety

In the pooled studies, there were no meaningful imbalances between the cyclosporine and the vehicle group in the incidence of treatment emergent adverse events (TEAEs) overall, and of ocular and nonocular TEAEs. There were 117 (20%) patients with TEAEs (of which 77 [13.2%] were ocular) in the cyclosporine arm and 117 (20.3%) patients with TEAEs (of which 76 [13.2%] were ocular) in the vehicle arm. Serious adverse events (SAEs) were reported by 8 participants (0.7%): 2 participants (0.3%) in the cyclosporine group and 6 participants (1.0%) in the vehicle group. For all of the SAEs, the relationship was assessed as not suspected to be related to study drug. None of the AEs reported resulted in death.

The only single AE term reported in more than 5% of participants overall was instillation site pain occurring in approximately 8.0% of participants in the ciclosporin 0.1% groups. The only other term occurring in more than 1% of participants was visual acuity reduced.

## DISCUSSION

The importance of treating corneal punctate epithelial keratitis preoperatively has been emphasized previously.[5,9] This is even more critical if the visual axis is affected. An early onset and clinically meaningful magnitude of effect, as observed with this water-free cyclosporine 0.1% solution, is a key factor in preoperative decision-making because delaying surgery is not desirable by the patient or the surgeon.

This pooled analysis of the ESSENCE-1 and ESSENCE-2 study data evaluated the efficacy of the first water-free topical cyclosporine 0.1% solution in patients with DED diagnosed with cataract in comparison with patients without cataract and pseudophakic patients. The overall population in the 2 trials was characterized as predominately aqueous-deficient DED patients with corneal epithelial damage that affected the central area of the cornea, which translated into vision-related symptoms. The 3 subgroups were comparable in their DED characteristics but showed expected differences regarding age and visual acuity: pseudophakic patients and patients with clinically significant cataract were older and had worse vision.

Higher absolute improvements in tCFS from baseline in patients without cataract compared with the other 2 groups

can likely be attributed to differences in age, hence less disease duration. The changing microenvironment of the ocular surface with age has been well described.[18] These age-related changes of the ocular surface may potentially influence treatment outcomes. When data were analyzed by age (≥65 years vs <65 years), the younger patients also showed higher mean improvements from baseline compared with older patients. Within each subgroup, the cyclosporine 0.1% arm was superior to the vehicle arm. In addition, older age might mean longer disease duration and more chronic inflammation potential with irreversible changes in the lacrimal functional unit. These findings are consistent with preclinical experimental DED models showing that younger mice responded earlier and with larger effect to treatment compared with older mice.[19]

Results of the pooled analysis showed that all 3 subgroups benefited from the treatment with cyclosporine 0.1% solution. In the DED group with concomitant cataract, the average decrease in tCFS in the cyclosporine group was clinically meaningful, with an average improvement of 3.2 severity grades (0 to 15) and 56.3% of patients showing a response of ≥ 3 grade at day 15.

Improvement in the corneal staining endpoint has previously been reported with other FDA-approved dry eye treatments. Lifitegrast showed improvements on the ocular surface after 12 weeks and cyclosporine emulsion 0.05% after 16 weeks of treatment.[20,21] A previous study using 0.09% cyclosporine nanoemulsion formulation reported earlier onset of effect on corneal staining; however, the magnitude of effect seemed modest (mean improvement, −1.1 from baseline [modified NEI; 0 to 20]) at day 14.[22] Open-label studies indicate that treatment with lifitegrast and the 0.09% cyclosporine nanoemulsion improved the predictive power for intraocular lens implants in patients with concomitant dry eye and also an improvement of corneal staining after short-term therapy.[23,24]

Owing to their perceived fast onset of effect, topical steroids are frequently used to treat ocular surface disease before keratorefractive or phacorefractive surgery. However, randomized controlled trials demonstrating improvements of ocular surface staining for topical steroids are rare.[25] Loteprednol etabonate 0.5% vs its vehicle administered 4 times daily showed no statistically significant difference between the treatment arms in corneal staining score with mean change from baseline of −7.4% in the loteprednol-treated arm and −9.7% in the subgroup with a higher corneal staining score (≥10, comparable with participants in the current investigation).[26] The improvement in corneal staining score in this study was −33.9% in the overall population of this pooled analysis. A mucus-penetrating loteprednol etabonate 0.25% formulation administered 4 times daily reported significant improvement in tCFS score against vehicle in 2 of the 3 trials, albeit without data on magnitude of effect.[27]

Based on the review of currently used treatment options and results presented in the pooled analysis, this new water-free cyclosporine 0.1% solution may be a promising treatment to improve the ocular surface before cataract surgery. The observed clinical effects are the result of the formulation combining the anti-inflammatory effect of cyclosporine with unique physical properties of the vehicle such as excellent spreading, lubrication of the ocular surface, and reduction of shear forces. Further studies evaluating the correlation of improvement in corneal punctate epithelial keratitis on preoperative biometry before cataract surgery and the precision of postsurgical refractive outcomes are needed.

The new water-free cyclosporine 0.1% solution demonstrated rapid and clinically meaningful improvement in corneal punctate epithelial keratitis in patients with dry eye and concomitant cataract. This treatment should be considered in the preoperative management of ocular surface disease in patients who are candidates for cataract surgery.

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