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# Efficacy and Safety of a Water-Free Topical Cyclosporine, 0.1%, Solution for the Treatment of Moderate to Severe Dry Eye Disease
## The ESSENCE-2 Randomized Clinical Trial

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**IMPORTANCE** Dry eye disease (DED) is a common public health problem with significant impact on vision-related quality of life and well-being of patients. Medications with rapid onset of action and a good tolerability profile remain an unmet need.

**OBJECTIVE** To assess efficacy, safety, and tolerability of a water-free cyclosporine ophthalmic solution, 0.1% (CyclASol [Novaliq GmbH]), applied twice daily in DED compared with vehicle.

**DESIGN, SETTING, AND PARTICIPANTS** CyclASol for the Treatment of Signs and Symptoms of Dry Eye Disease (ESSENCE-2) was a phase 3, multicenter, randomized, double-masked, vehicle-controlled clinical study conducted from December 5, 2020, to October 8, 2021. Following a 14-day run-in period with an artificial tear administered 2 times per day, eligible participants were randomly assigned 1:1 to the treatment groups. Patients with moderate to severe DED were included in the study.

**INTERVENTIONS** Cyclosporine solution vs vehicle administered 2 times per day for 29 days.

**MAIN OUTCOMES AND MEASURES** The primary end points were changes from baseline in total corneal fluorescein staining (tCFS; 0-15 National Eye Institute scale) and in dryness score (0-100 visual analog scale) at day 29. Conjunctival staining, central corneal fluorescein staining, and tCFS responders were also assessed.

**RESULTS** A total of 834 study participants were randomly assigned to cyclosporine (423 [50.7%]) or vehicle (411 [49.3%]) groups at 27 sites. Participants had a mean (SD) age of 57.1 (15.8) years, and 609 (73.0%) were female individuals. The majority of participants self-identified in the following race categories: 79 Asian (9.5 %), 108 Black (12.9%), and 635 White (76.1%). Participants treated with cyclosporine solution had greater improvement in tCFS (−4.0 grades) than the vehicle group (−3.6 grades) at day 29 (change [Δ] = −0.4; 95% CI, −0.8 to 0; $P$ = .03). The dryness score showed treatment benefits from baseline in both groups: −12.2 points for cyclosporine and −13.6 points for vehicle (Δ = 1.4; 95% CI, −1.8 to 4.6; $P$ = .38). In the cyclosporine group, 293 participants (71.6%) achieved clinically meaningful reductions of 3 grades or higher in tCFS vs 236 (59.7%) in the vehicle group (Δ = 12.6%; 95% CI, 6.0%-19.3%; $P$ < .001). These responders showed greater improvement in symptoms at day 29 including dryness (Δ = −4.6; 95% CI, −8.0 to −1.2; $P$ = .007) and blurred vision (Δ = −3.5; 95% CI, −6.6 to −4.0; $P$ = .03) compared with nonresponders.

**CONCLUSIONS AND RELEVANCE** The ESSENCE-2 trial confirmed that treatment with a water-free cyclosporine solution, 0.1%, results in early therapeutic effects on the ocular surface compared with vehicle. The responder analyses suggest that the effect is clinically meaningful in 71.6% of participants in the cyclosporine group.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT04523129

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Visual Abstract

Invited Commentary
page 466

Supplemental content

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Dry eye disease (DED) is one of the most common ocular disorders with more than 16 million Americans having physician-diagnosed DED.[1,2] Inflammation and immunologic processes play a key role in the pathology of this disease.[3] DED is marked by changes in ocular surface and tear film parameters and accompanied by eye discomfort and blurred vision symptoms.[4] A compromised ocular surface secondary to DED may also compromise refractive measurements before keratorefractive and phacorefractive surgeries and adversely impact postoperative visual outcomes.[5-9] There is no criterion standard for DED disease management. A staged management according to severity of physician-measured findings is recommended.[10,11] Prescription eye drops, cyclosporine, lifitegrast, or short-term corticosteroid are initiated when a patient does not improve with over-the-counter artificial tears, eyelid hygiene measures, and modification of environmental factors. Patients with a preoperative compromised ocular surface also need prescription topical treatment for rapid restoration of the ocular surface before their vision-correcting surgery.[5] There is a high unmet need for effective treatments that can provide rapid and clinically meaningful improvements of the corneal surface and are well tolerated.

The treatment under investigation contains cyclosporine, 0.1%, which is a potent anti-inflammatory and immunomodulatory drug. Although not water-soluble, cyclosporine is soluble in the water-free excipient perfluorobutylpentane (often abbreviated F4H5), forming a clear solution free of oils, surfactants, and preservatives. Cyclosporine is less soluble in a related compound, perfluorohexyloctane, which is already used in the management of DED. The higher concentration and the preservative-free formulation provide improved bioavailability and efficacy on the target tissue as well as better tolerability.[12-14] In a phase 2 dose-finding study, this novel formulation showed a consistently larger reduction in corneal and conjunctival staining compared with both vehicle and cyclosporine, 0.05%, emulsion ([Restasis] AbbVie) over the 16-week treatment period, with an early onset of effect, noticeable after 2 weeks of treatment. The central region of the cornea benefitted the most.[15] The subsequent, first pivotal phase 2b/3 study, CyclASol for the Treatment of Dry Eye Disease (ESSENCE-1 [CYS-003]), confirmed the effects on corneal and conjunctival staining. In addition, the study showed statistically significant improvements in the dryness score compared to its vehicle.[16]

This work presents the results of the second pivotal phase 3 study, CyclASol for the Treatment of Signs and Symptoms of Dry Eye Disease (ESSENCE-2 [CYS-004]), designed to confirm the efficacy, safety, and tolerability of cyclosporine, 0.1%, solution in comparison with its novel water-free vehicle for the treatment of the signs and symptoms of DED.

## Key Points

**Question** Is a water-free cyclosporine eye drop, 0.1%, effective in treating dry eye disease (DED)?

**Findings** In this randomized, double-masked, vehicle-controlled, clinical trial including 834 study participants with moderate to severe DED, cyclosporine solution, 0.1%, was effective in treating dry eye–related keratitis and was well tolerated. The total and central corneal staining score showed improvements after only 2 weeks of treatment, with persistent efficacy through day 29.

**Meaning** The rapid onset and magnitude of improvements on the corneal epithelial damage are potential differentiators to existing therapies.

## Methods

### Study Design

The ESSENCE-2 trial was a randomized, double-masked, and vehicle-controlled clinical study to demonstrate the efficacy, safety, and tolerability of cyclosporine solution after 4 weeks of treatment. The study was performed at 27 clinical sites in the US from December 5, 2020, to October 8, 2021, in accordance with the Declaration of Helsinki and the International Conference on Harmonization guideline on Good Clinical Practices. The trial protocol is available in Supplement 1.

This study was reviewed and approved by the institutional review board Alpha IRB in San Clemente, California, and was reported according to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. Study participants received expense allowance. After written informed consent was obtained, study participants who met all eligibility requirements started with an open-label, 14-day run-in period using a commercially available artificial tear substitute ([Systane Balance] Alcon Laboratories Inc) dosed as 1 single eye drop per eye twice daily. Upon confirmation of the eligibility criteria, participants were randomly assigned to 1 of 2 treatment arms: cyclosporine, 0.1%, solution or vehicle. Randomization schedules were created by an unmasked statistician not otherwise involved. Participants returned for a follow-up visit on day 15 ± 2 and day 29 ± 2. Approximately 200 of the participants had the opportunity to roll over to a 1-year extension study, which will be reported separately.

During the treatment period, study participants were dosed 1 single eye drop per eye twice daily for 29 consecutive days. Concomitant use of artificial tears was not allowed. Both treatment arms used identical packaging and labeling. Investigators, study staff, and participants were all masked to study treatment.

### Assessment of Outcome Measures

Efficacy, safety, and tolerability outcome measures were assessed for both eyes at scheduled prespecified visits: visit 0 (screening; day −14 ± 2), visit 1 (baseline/randomization; day 1), visit 2 (day 15 ± 2), and visit 3 (day 29 ± 2). The 2 primary efficacy measures at day 29 in this trial were as follows: change from baseline in total corneal fluorescein staining (tCFS) and dryness score. tCFS was measured using the National Eye Institute (NEI) scale, which ranges from 0 (no staining) to 3 (heavy staining) for each of the 5 areas of the cornea (inferior, superior, central, nasal, and temporal). The total score ranging from 0 to 15 is the sum of the 5 regions. The dryness score was assessed by a visual analog scale (VAS), which is a patient-reported symptom index ranging from 0 for no discomfort to

100 for maximal discomfort. Other key secondary efficacy end points included (1) tCFS responders, defined as 3 grades or higher of improvement on the NEI scale at day 29; (2) change from baseline in tCFS on day 15; (3) change from baseline in central CFS at day 29; (4) central CFS responders, defined as 1 grade or higher of improvement in the central area of the cornea on the NEI scale at day 29; (5) change from baseline in conjunctival staining at day 29 using lissamine green dye according to Oxford grading scale (nasal and temporal regions were graded from 0-5 separately, and the total score was the sum of both regions); and (6) change from baseline in blurred vision score assessed using VAS at day 29.

Other secondary end points of the study were change from baseline in central CFS at day 15, conjunctival lissamine green staining score at day 15, and dryness and blurred vision scores at day 15. Compliance was assessed via a dosing diary.

### Study Participants

Participants met all inclusion criteria at screening and time of randomization including total CFS score of 10 or higher, dryness score of 50 or higher, total conjunctival staining score of 2 or higher, unanesthetized Schirmer I test score of 1 mm or greater and 10 mm or less at 5 minutes, and the current use of artificial tears. Participants self-identified with the following race and ethnicity categories: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. Race and ethnicity information is a regulatory requirement for pivotal studies to allow health agencies to assess if the population under study reflects the population of their country. Key exclusion criteria were clinically relevant abnormal slitlamp findings including significant blepharitis or meibomian gland dysfunction and conjunctival or corneal abnormalities. Participants with current use of contact lenses, intraocular surgery, or ocular laser surgery within 6 months prior to screening or treatment with topical cyclosporine or lifitegrast within 2 months prior to screening were excluded.

One eye with the highest tCFS of each study participant was designated as the study eye. If tCFS score of both eyes at baseline was the same, the right eye was designated as the study eye. Ocular symptoms were assessed per participant.

Treatment-emergent adverse events (TEAEs) were defined as AEs occurring after the first dose of randomized study treatment was administered. The investigator determined the severity and association with the study treatment.

### Statistical Methods

Sample size was calculated based on the following assumptions: for the mean change from baseline in tCFS (NEI scale) at day 29, a difference of −0.75 was assumed with an SD of 2.7, and for the mean change from baseline in dryness score at day 29, a difference of −5.0 was assumed, with an SD of 20.0. Under both assumptions, a sample size of approximately 380 participants per treatment group (for a total of 420 randomized participants per group, assuming 10% discontinuation rate) was chosen to yield greater than 90% power to detect a significant difference at the 2-sided $\alpha = .05$ level. The hierarchical testing was selected to protect the $\alpha$ error for the 2 primary end points. Change from baseline in tCFS was tested first.

The primary efficacy analysis was performed on the study eye of the full-analysis set on available data, which included all randomly assigned participants having received at least 1 dose of study treatment.

The primary efficacy analyses compared the mean change from baseline in tCFS score and in dryness score and were analyzed separately using an analysis of covariance (ANCOVA) model with terms for baseline value, site, and treatment group. Least squares mean for each treatment group and for the difference between treatment groups was presented from the model together with 2-sided *P* values and 95% CIs.

If both primary end points demonstrated statistical superiority, key secondary end points were also tested hierarchically to protect the $\alpha$ error. Quantitative secondary end points were analyzed using an analogous ANCOVA model. The responder end points were analyzed using a logistic regression model. Two-sided CIs and 2-sided *P* values for the difference of marginal proportions were reported from the logistic regression model. Data were analyzed using SAS software, version 9.4 or higher (SAS Institute).

## Results

### Study Participant Disposition

Twenty-seven clinical sites screened 1879 patients, of whom 834 were enrolled. There were 423 participants (50.7%) randomly assigned to the cyclosporine group and 411 (49.3%) to the vehicle group.

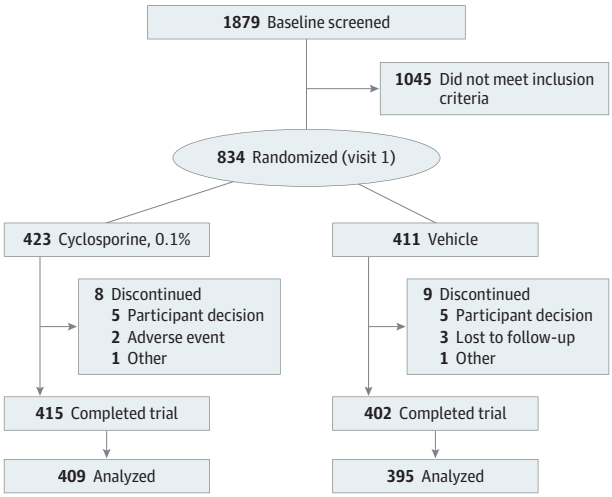
A total of 817 participants (98.0%) completed the study. Seventeen participants (2.0%) discontinued treatment: 8 (1.9%) in the cyclosporine group and 9 (2.2%) in the vehicle group (**Figure 1**). Both participants that withdrew from the study due to AEs were in the cyclosporine group; 1 reported instillation site burning, and the other had cholelithiasis.

### Baseline Characteristics

Demographic characteristics of age, sex, disease duration, and baseline dry eye parameters were well balanced between the treatment groups (**Table 1**). Participants had a mean (SD) age of 57.1 (15.8) years; 609 were female individuals (73.0%), and 225 were male individuals (27.0%). Participants self-identified with the following race and ethnicity categories: 2 American Indian or Alaska Native (0.2%), 79 Asian (9.5%), 108 Black or African American (12.9%), 1 Native Hawaiian or Other Pacific Islander (0.1%), and 635 White (76.1%). Other than DED, the most common ocular comorbidity was cataract (34% [286]), and 19% (158) of the participants had pseudophakia.

In total, 21 major protocol deviations were recorded: 12 deviations were due to study visits being significantly out of window (ie, measurements of the primary end point were performed more than 7 days outside of the visit window [day 29 ± 2 days]), 5 were deviations of inclusion/exclusion criteria, 2 study participants took prohibited concomitant medication, 2 were related to study drug assignment, and 2 participants

Figure 1. Study Participant Disposition Comparing the Efficacy and Safety of a Water-Free Cyclosporine, 0.1%, Solution vs Vehicle in the Treatment of Moderate to Severe Dry Eye Disease




Key reasons for screen failure were not meeting inclusion criteria due to the severity of dryness (n = 339), total corneal fluorescein staining score (n = 196), and previous use of artificial tears (n = 154). Participants who had missing data or visits out of window (eg, participants had their assessments taken 7 days or more outside the visit window for the primary end point [day 29 ±2]) were not considered for analyses.

were noncompliant (self-administering <80% of expected doses per dosing diary).

## Efficacy

### Primary End Points

At day 29, a larger improvement in tCFS from baseline was observed in the cyclosporine group with −4.0 grades reduction compared with −3.6 in the vehicle group (change [Δ] = −0.4; 95% CI, −0.8 to 0; $P$ = .03) (**Table 2**). A sensitivity analysis including all qualifying eyes was conducted showing a tCFS reduction of −3.8 and −3.3 grades in the cyclosporine and vehicle group, respectively (Δ = −0.5; 95% CI, −0.8 to −0.1; $P$ = .007).

The second hierarchically tested primary symptom end point, dryness score, improved from baseline in both groups, with −12.2 points in the cyclosporine group and −13.6 points in the vehicle group (Δ = 1.4; 95% CI, −1.8 to 4.6; $P$ = .38) (Table 2).

All secondary sign end points including central CFS, central CFS responders, conjunctival staining, and tCFS at day 15 showed better outcomes with the cyclosporine treatment compared with vehicle (Table 2). Within 4 weeks, 293 participants (71.6%) treated with cyclosporine responded with an improvement of 3 grades or higher in tCFS vs 236 participants (59.7%) in the vehicle group (Δ = 12.6%; 95% CI, 6.0%-19.3%; $P$ < .001). These tCFS responders irrespective of treatment showed improvements at day 29 for a variety of symptoms compared with nonresponders including dryness (responder, −14.7; nonresponder, −10.1; Δ = −4.6; 95% CI, −8.0 to −1.2; $P$ = .007), blurred vision (responder, −7.8; nonresponder, −4.2; Δ = −3.5; 95% CI, −6.6 to −0.4; $P$ = .03), difficulty looking at screens (responder, −9.7; nonresponder, −5.3; Δ = −4.4; 95% CI, 7.8 to −1.1; $P$ = .009), and difficulty driving at night (responder, −8.9; nonresponder, −4.2; Δ = −4.7; 95% CI, −8.4 to −1.1; $P$ = .01), reflecting the clinical relevance of 3 grades or higher of corneal surface staining improvement (**Figure 2** and eFigure in Supplement 2).

Reductions from baseline in the blurred vision score were seen in both groups, with a −7.1-point reduction in the cyclosporine group and a −6.1-point reduction in the vehicle group at day 29 (Δ = −1.0; 95% CI, −4.0 to 2.0; $P$ = .51) (Table 2).

In a post hoc analysis of the subgroup of participants with high central CFS scores (cCFS = 3) at baseline, the cyclosporine group showed greater reductions in blurred vision score (−11.7) compared with the vehicle group (−4.6) at day 29 (Δ = −7.0; 95% CI, −13.2 to −0.8; $P$ = .03).

Table 1. Demographic and Baseline Characteristics

| Characteristic | No. (%) Cyclosporine, 0.1% (n = 423) | Vehicle (n = 411) |
|---|---|---|
| Age, mean (SD), y | 57.6 (15.36) | 56.6 (16.30) |
| ≥65 | 157 (37.1) | 150 (36.5) |
| Sex[a] | | |
| Male | 117 (27.7) | 108 (26.3) |
| Female | 306 (72.3) | 303 (73.7) |
| Race and ethnicity[a] | | |
| American Indian or Alaska Native | 2 (0.5) | 0 |
| Asian | 40 (9.5) | 39 (9.5) |
| Black or African American | 53 (12.5) | 55 (13.4) |
| Native Hawaiian or Other Pacific Islander | 1 (0.2) | 0 |
| White | 323 (76.4) | 312 (75.9) |
| Dry eye disease duration, y | | |
| Mean (SD) | 10.3 (9.55) | 10.4 (10.32) |
| ≥10 | 162 (38.3) | 155 (37.7) |
| Baseline ocular characteristics, mean (SD) | | |
| tCFS (NEI) at baseline | 11.5 (1.41) | 11.5 (1.36) |
| cCFS (NEI) at baseline | 2.1 (0.63) | 2.1 (0.63) |
| Conjunctival staining | 3.7 (1.72) | 3.8 (1.67) |
| VAS severity of dryness at baseline | 70.4 (12.53) | 70.0 (12.59) |
| VAS blurred vision at baseline | 53.4 (26.56) | 51.9 (29.97) |
| Schirmer score at baseline | 5.1 (2.96) | 4.8 (2.78) |

Abbreviations: cCFS, central corneal fluorescein staining; NEI, National Eye Institute; tCFS, total corneal fluorescein staining; VAS, visual analog scale.

[a] Sex and race as self-reported by study participants.

## Safety

A total of 144 of 834 participants (17.3%) reported 178 TEAEs during the study. The number of participants reporting at least 1 TEAE or ocular TEAE were similar between the 2 study groups: 71 (16.8%) and 57 (13.5%) in the cyclosporine group and 73 (17.8%) and 62 (15.1%) in the vehicle group, respectively. The most common ocular TEAEs were installation-site reactions in the cyclosporine group (43 [10.2%]) and in the vehicle group (36 [8.8%]). These were all mild except for 1 case in each group (**Table 3**).

Table 2. Main Outcome Measures[a]

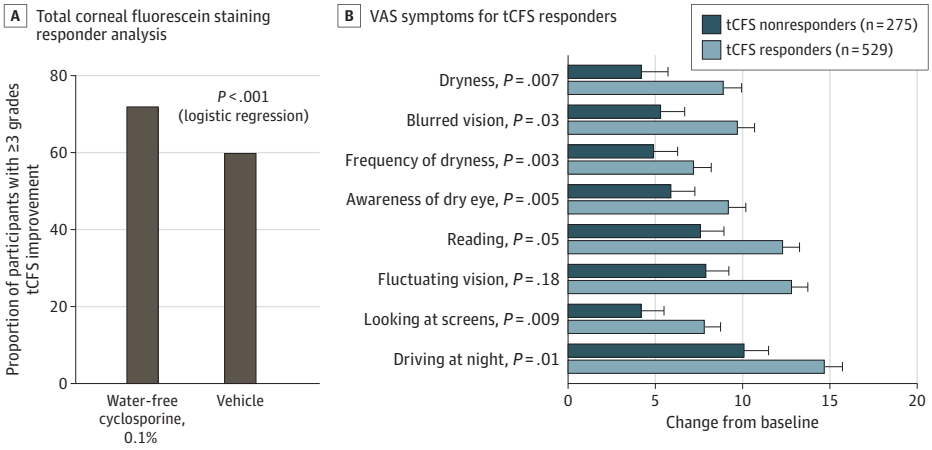
| Measures | Day | Change from baseline, LS mean: Cyclosporine, 0.1% | Vehicle | Group difference, LS mean (95% CI)[b] | *P* value |
|---|---|---|---|---|---|
| Primary | | | | | |
| tCFS | 29 | −4.0 | −3.6 | −0.4 (−0.8 to −0.0) | .03 |
| Dryness score | 29 | −12.2 | −13.6 | 1.4 (−1.8 to 4.6) | .38 |
| Key secondary | | | | | |
| Conjunctival staining | 29 | −1.2 | −0.9 | −0.3 (−0.5 to −0.1) | .001 |
| cCFS | 29 | −0.8 | −0.7 | −0.1 (−0.2 to 0.0) | .04 |
| tCFS | 15 | −3.5 | −3.0 | −0.6 (−0.9 to −0.2) | .002 |
| Blurred vision (VAS) | 29 | −7.1 | −6.1 | −1.0 (−4.0 to 2.0) | .51 |
| | | Observed response rates, % | | | |
| cCFS responder (≥1 grade improvement) | 29 | 67.2 | 60.3 | 7.3% (0.3 to 14.4) | .04 |
| tCFS responder (≥3 grade improvement) | 29 | 71.6 | 59.7 | 12.6% (6.0 to 19.3) | <.001 |
| Secondary | | | | | |
| Conjunctival staining | 15 | −0.9 | −0.7 | −0.1 (−0.3 to 0.1) | .19 |
| cCFS | 15 | −0.7 | −0.6 | −0.2 (−0.3 to −0.1) | .005 |
| Dryness score | 15 | −7.5 | −9.6 | 2.1 (−0.5 to 4.8) | .12 |
| Blurred vision (VAS) | 15 | −5.7 | −5.2 | −0.5 (−3.1 to 2.1) | .70 |

Abbreviations: cCFS, central corneal fluorescein staining; LS, least square; tCFS, total corneal fluorescein staining; VAS, visual analog scale.

[a] Day 15: cyclosporine, 0.1%, group = 418 participants; vehicle group = 403 participants; day 29: cyclosporine, 0.1%, group = 409 participants; vehicle group = 395 participants.

[b] 95% CI on day 29.

Figure 2. Total Corneal Fluorescein Staining (tCFS) at Day 29 Responder Analysis and Visual Analog Scale (VAS) Symptoms for tCFS Responders




A, Proportion of corneal fluorescein staining responders (≥3 score improvement on the National Eye Institute scale) at day 29 using a water-free cyclosporine, 0.1%, solution vs vehicle in the treatment of moderate to severe dry eye disease. B, Improvement in symptoms in tCFS responders vs nonresponders irrespective of treatment.

Five serious TEAEs (SAEs; 2 [0.5%] in the cyclosporine group and 3 [0.7%] in the vehicle group) were reported during the trial. All SAEs were assessed as not associated with the study drug. Across both treatment groups, no significant changes from baseline were observed by slitlamp biomicroscopy, dilated ophthalmoscopy, visual acuity, or intraocular pressure.

### Comfort and Treatment Satisfaction

Cyclosporine solution was comfortable on instillation, with a mean comfort score of 2.5 or less (0-10 scale; 0 = very comfortable and 10 = very uncomfortable) in both groups. Positive descriptors were frequently selected by participants in both treatment groups, with more than 80% of participants selecting 1 or more positive descriptors, of which the 3 most-frequently selected descriptors were comfortable, smooth, and soothing.

At the end of the study, participants were asked "How satisfied are you with the eye drop?" A total of 24% of participants (204), irrespective of the treatment, rated the question with 10 (the highest satisfaction rate); 78% (653) rated with 5 or higher.

## Discussion

This second phase 3 clinical study ESSENCE-2 (CYS-004) was designed to confirm efficacy, safety, and tolerability of a water-free cyclosporine, 0.1%, ophthalmic solution for the treatment of DED compared with its vehicle.

Table 3. Summary of Ocular Treatment-Emergent Adverse Events (TEAEs)

| TEAEs | No. (%) | |
|---|---|---|
| | Cyclosporine 0.1% (n = 423) | Vehicle (n = 411) |
| Ocular and nonocular AEs | | |
| TEAEs, No. | 82 | 96 |
| Participants with at least 1 TEAE | 71 (16.8) | 73 (17.8) |
| TE serious AEs | 2 (0.5) | 3 (0.7) |
| Participants discontinued treatment due to an AE | 2 (0.5) | 3 (0.7) |
| Ocular AEs | | |
| TEAEs, No. | 68 | 75 |
| Participants with at least 1 TEAE | 57 (13.5) | 62 (15.1) |
| Ocular AEs that occurred in more than 2% of study participants | | |
| Visual acuity reduced | 7 (1.7) | 13 (3.2) |
| Instillation site reactions | | |
| Mild | 42 (9.9) | 35 (8.5) |
| Moderate | 1 (0.2) | 1 (0.2) |
| Severe | 0 | 0 |
| Vision blurred | 2 (0.5) | 2 (0.5) |

A low average Schirmer tear production test score and high average corneal staining and ocular symptom score characterize the study population as patients with moderate to severe predominantly aqueous-deficient DED. Of note, 35% of patients had a coexisting cataract. The importance of this is that many of these patients are candidates for cataract surgery. A compromised ocular surface and punctate erosions of the cornea may lead to inaccurate biometry measurements before the procedure and postoperative dissatisfaction.[5-9]

The ESSENCE-2 study demonstrated superiority to vehicle in the primary sign end point tCFS score at day 29, thereby confirming ESSENCE-1 results.[16] In addition, the onset of effect in tCFS reached statistical significance at day 15, which is substantially faster than reported results with other products used for the treatment of DED.[17-21]

To our knowledge, there is little information available regarding which between-group difference in staining outcomes is clinically relevant. Therefore, this study included a responder analysis for tCFS to evaluate whether the results were clinically meaningful. A responder was defined as having an improvement of 3 grades or higher on the NEI scale, which was selected based on published literature[22,23] and feedback from treating clinicians who consider such a difference immediately noticeable and clinically relevant. Given that the NEI scale is not linear, a difference of 1 grade in a subregion typically corresponds to a 3-fold difference of punctate staining in the respective subregion.[24] In the cyclosporine group, a greater proportion (71.6%) of participants were tCFS responders compared with vehicle group (59.7%), and this difference was statistically significant. Further, our analysis demonstrated that 3 grades or higher of improvement in tCFS was associated with significant improvements in a variety of symptom end points, showing that such a magnitude of improvement in the physician-measured signs is correlated with patient-reported symptoms.

Corneal staining was recently proposed as a single, standard, objective dry eye outcome measure across clinical studies based on mounting evidence regarding its association with measurable visual function and vision-related quality-of-life outcomes.[25] Additionally, the American Society of Cataract and Refractive Surgery views corneal staining as the single most critical sign that should be normalized prior to any form of vision-related surgery.[5] To our knowledge, the rapidity of the onset as well as the magnitude of effect of cyclosporine, 0.1%, solution on corneal staining has not been shown with other approved therapies.[21] In current practice, topical steroids are also frequently used to treat the ocular surface before keratorefractive or phacorefractive surgery because of the notion that they improve corneal findings rapidly.[5] However, randomized clinical trials demonstrate conflicting results for steroids and even in studies with favorable results, the magnitude of effect appears smaller than that observed in the present study.[10,26,27]

The water-free vehicle comparator in this preparation, perfluorobutylpentane, appears to be an ideal and comfortable carrier of cyclosporine for topical delivery. This compound itself provides considerable improvement in dry eye signs and symptoms,[15] potentially providing an explanation as to why the treatment effects in symptoms did not reach statistical significance in the overall population.

Study participants with high central corneal staining at baseline benefitted from cyclosporine, 0.1%, treatment with greater improvements in their blurred vision symptom compared with vehicle. This improvement is likely secondary to the improvement in corneal staining as punctate erosions in the central cornea cause blurring of the image reflected onto the retina that can affect visual acuity and contrast sensitivity.[7,28-30]

The relatively small number of AEs were similar between treatment groups and mostly of mild severity. Instillation-site reactions were low, and eye drop comfort assessment was favorable and comparable between the 2 groups. This tolerability profile addresses an unmet need in DED therapy. Real-world data for lifitegrast and cyclosporine, 0.05%, emulsion suggest that 12-month discontinuation rates are high: 64.4% for patients using lifitegrast and 70.8% for patients using cyclosporine, 0.05%, emulsion.[31] Installation-site reactions (25% for lifitegrast and 17% for cyclosporine, 0.05%, emulsion) and late-onset of efficacy are considered the key factors for these observations.

## Limitations

One limitation of our study is the inclusion of patients with predominantly aqueous-deficient DED, which might mean that the observed outcomes may not be generalizable to all patients with DED. Other limitations are the short duration of the treatment and lack of comparison with other approved topical treatments. A 52-week open-label study (CYS-005) was carried out, and the favorable long-term efficacy and safety of cyclosporine solution in DED will be reported separately. Longer-term studies against cyclosporine, 0.05%, emulsion or lifitegrast may be beneficial.

## Conclusions

The ESSENCE-2 randomized clinical trial demonstrated that a water-free cyclosporine solution is efficacious in improving ocular surface staining associated with DED compared with its vehicle. Rapidity and the magnitude of improvements on the corneal epithelial damage are potential differentiators to existing therapies. More data from clinical practice would be beneficial in understanding the potential of this treatment.

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**Author Contributions:** Dr Akpek had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Akpek, Wirta, Sheppard, Meides, Krösser.
*Acquisition, analysis, or interpretation of data:* Wirta, Downing, Tauber, Ciolino, Meides, Krösser.
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*Statistical analysis:* Krösser.
*Administrative, technical, or material support:* Akpek, Downing, Sheppard, Ciolino.
*Supervision:* Akpek, Wirta, Sheppard, Ciolino, Meides, Krösser.

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Invited Commentary

# Comparison of Water-Free Commercially Available Cyclosporine Ophthalmic Preparations—Different, but the Same

Andrea Naranjo Lozano, MD; Alice Shen, MD; Jennifer Rose-Nussbaumer, MD

**In this *JAMA Ophthalmology* edition,** Akpek et al[1] present a randomized, double-masked, vehicle-controlled trial to evaluate the efficacy, safety, and tolerability of a water-free cyclosporine, 0.1%, ophthalmic solution (CyclASol [Novaliq]) compared with its vehicle for moderate to severe dry eye. We must congratulate Akpek et al[1] for their nicely designed trial, promising findings, and enduring attempt to find alternative treatments for this widespread problem.

Related article page 459

Topical cyclosporine, 0.05%, ophthalmic emulsion (Restasis [Allergan]) has been approved by the US Food and Drug Administration since 2002. However, there are numerous limitations associated with this eye drop, including high cost, low concentration of active ingredient leading to reduced efficacy, and burning and stinging upon instillation, which can lead to poor medication compliance.[2] Animal studies have demonstrated that cyclosporine in perfluorobutylpentane can form a clear solution with improved bioavailability, efficacy, and tolerability.[3] This was clinically evidenced in a previous study when water-free cyclosporine (0.1% and 0.05%) was compared with the commercially available cyclosporine ophthalmic emulsion 0.05%. Water-free cyclosporine achieved a statistically significant reduction in corneal and conjunctival staining compared with both vehicle and commercially available cyclosporine ophthalmic emulsion over the 16-week treatment period, with an early onset of effect (at day 14).[4]

The results of this second trial, designed to confirm the outcomes of the first, are also encouraging. They report statistically significant improvement in the total corneal fluorescein staining among patients with aqueous-deficiency dry eye as early as 2 weeks with water-free cyclosporine, 0.1%, when compared with vehicle. However, in their trial design, they have 2 primary outcomes that are likely highly correlated. Best practice would be to define only 1 primary outcome or to split the *P* value between the 2 primary outcomes, resulting in an α of .025 for each. Neither of the 2 primary outcomes in the study by Akpek et al[1] would have been statistically significant if they had split the *P* value. They did use hierarchical testing to preserve their α for the 2 primary outcomes but did not give specifics about whether this was a prespecified approach or their exact methodology.

Although there were several other secondary outcomes that showed improvement with water-free cyclosporine, 0.1%, the clinical significance of these findings is unclear. The lack of association between dry eye signs and symptoms is a well-known phenomenon. Neither the Ocular Surface Disease Index (OSDI) score or dryness score achieved a statistically significant difference when compared with vehicle. Only those participants classified as responders, with at least a 3-grade improvement on the National Eye Institute scale, had improvement in reported symptoms more often with medication vs vehicle alone.

Lastly, medical treatment of dry eye has become extraordinarily expensive for ophthalmology patients. Water-free cyclosporine, 0.1%, may represent a marginal improvement over commercially available cyclosporine ophthalmic emulsion. However, many corneal specialists use compounded cyclosporine of 0.5% to 1.0% concentration because of concern that a low concentration of cyclosporine also results in low treatment efficacy. As acknowledged by the authors, a longer-term study comparing water-free cyclosporine, 0.1%, to other established dry eye therapies such as topical steroids, autologous serum tears, or lifitegrast is warranted. One wonders what the cost of this new eye drop will be when the main improvement appears to be a superior vehicle? Novel treatment modalities for dry eye that are accessible to ophthalmology patients are greatly needed.

ARTICLE INFORMATION

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