Cyclosporine ophthalmic solution 0.09% improves the signs and symptoms of dry eye disease in patients whose disease is inadequately controlled on cyclosporine ophthalmic emulsion 0.05%

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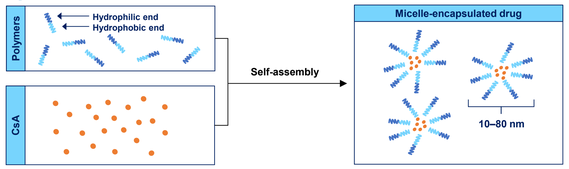
INTRODUCTION

- Dry eye disease (DED) is a multifactorial ocular surface disorder characterized by loss of tear film homeostasis, hyperosmolarity, and tear film instability that perpetuates ocular surface inflammation and damage[1,2]
- Cyclosporine ophthalmic solution 0.09% (CsA 0.09%) and cyclosporine ophthalmic emulsion 0.05% (CsA 0.05%) are immunomodulatory agents that treat the underlying ocular surface inflammation characteristic of DED and are both indicated to increase tear production in affected patients[3,4]
- CsA 0.09% is a novel, nanomicellar solution of cyclosporine A (**Figure 1**) designed to improve drug delivery to the ocular surface while minimizing ocular adverse reactions[5]
- This study assessed the efficacy and patient-reported outcomes associated with CsA 0.09% treatment in patients with DED that was inadequately controlled on CsA 0.05%

Figure 1. Nanomicellar formulation of cyclosporine ophthalmic solution 0.09%



METHODS

Study design

- This was a Phase 4, multicenter, open-label, single-arm study
- All patients administered 1 drop of CsA 0.09% in both eyes twice daily for 12 weeks

Study population

- Enrolled patients were adults with DED that was not adequately controlled (still symptomatic and/or exhibiting signs of disease) by current treatment with CsA 0.05% for ≥3 months
- Key eligibility criteria
  - A history and clinical diagnosis of DED for ≥3 months at screening/baseline
  - At least 1 of the following at screening/baseline:
    - A total corneal fluorescein staining (CFS) score ≥6 (range, 0–20) or score ≥2 in an individual zone (range, 0–4) in ≥1 eye
    - A modified Symptom Assessment iN Dry Eye (mSANDE) global symptom score of ≥40 (range, 0–100)
  - A best-corrected visual acuity of 20/200 or better in both eyes at screening/baseline
  - Discontinuation of all other topical ocular medications or DED therapies other than artificial tears and lid scrubs if used routinely and initiated ≥1 month before screening/baseline
- Exclusion criteria
  - Use of CsA 0.05% in both eyes for a period shorter than 3 months before screening/baseline
  - A history of treatment failure with CsA 0.05% or previous discontinuation of or switching from CsA 0.05%
  - Active ocular disease other than DED in either eye
  - Use/initiation of any systemic or topical ocular medication known to cause/exacerbate DED within 7 days prior to screening/baseline or during the study, such as:
    - Immunomodulators, antihistamines, cholinergics, antimuscarinics, antidepressants, phenothiazines, retinoids, or topical ocular or systemic corticosteroids

Outcome measures

- Efficacy endpoints included central CFS, Schirmer's test, the mSANDE questionnaire, and frequency of artificial tear use
  - Patients also reported their treatment preference at the end of the study on Week 12 for CsA 0.09% or their previous treatment with CsA 0.05%
- Safety was assessed by recording of adverse events (AEs)

Assessments

- Assessments for each efficacy outcome were made at screening/baseline and then at Weeks 4, 8, and 12, and/or on early termination
  - Central CFS was assessed from 2 to 2.5 minutes after instilling 1 drop of 0.5% sodium fluorescein into each eye and was scored on a modified National Eye Institute grading scale from 0 to 4 in 0.5-point increments (0, no stain; 4, severe stain)
  - Schirmer's test strips were placed in both eyes for 5 minutes and the amount of wetting was recorded in millimeters
  - The mSANDE instrument is a 2-question assessment quantifying the frequency and severity of DED symptoms of dryness and irritation on a 0- to 100-mm linear visual analog scale, where 0 = very low symptom frequency/severity and 100 = very high symptom frequency/severity
    - The global symptom score (√[frequency score × severity score]) was calculated at each visit
  - Frequency of artificial tear product use was recorded daily by patients and reviewed at each study visit
- Patients also reported their treatment preference at the end of the study for CsA 0.09% or their previous treatment with CsA 0.05%

Statistical analysis

- Continuous variables were summarized with descriptive statistics (n, mean, median, standard deviation [SD], standard error, minimum, and maximum), and categorical variables were summarized with counts and percentages
- The change from baseline was evaluated using the 2-tailed Student's t-test

RESULTS

Patient demographics

- A total of 124 patients were included in the intent-to-treat population (received ≥1 dose of CsA 0.09% and had ≥1 postbaseline assessment; **Table 1**)

Table 1. Patient demographics

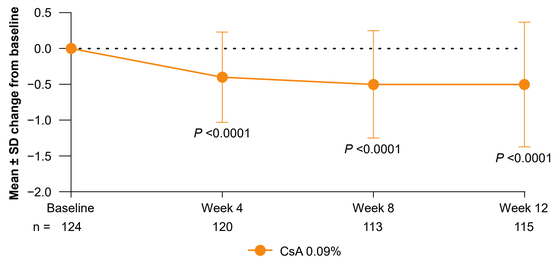
	All patients[a] N = 124
Age, years, mean ± SD	65.6 ± 11.54
Sex, female, n (%)	109 (87.9)
Race, n (%)	
White	109 (87.9)
Black or African American	10 (8.1)
Asian	4 (3.2)
Other	1 (0.8)
Ethnicity, n (%)	
Hispanic/Latino	17 (13.7)
Not Hispanic/Latino	107 (86.3)

[a]Data are presented for the intent-to-treat population, which includes all patients who received ≥1 dose of study medication and had ≥1 postbaseline assessment.
SD, standard deviation.

Central corneal fluorescein staining

- The mean ± SD baseline central CFS score was 0.8 ± 0.9
- Mean central CFS scores decreased over time and the mean ± SD change from baseline at Week 12 was −0.5 ± 0.9 (*P* <0.0001; **Figure 2**)
  - Mean changes from baseline in central CFS score were also statistically significant at Weeks 4 and 8 (*P* <0.0001)

Figure 2. Mean change from baseline in central fluorescein staining scores

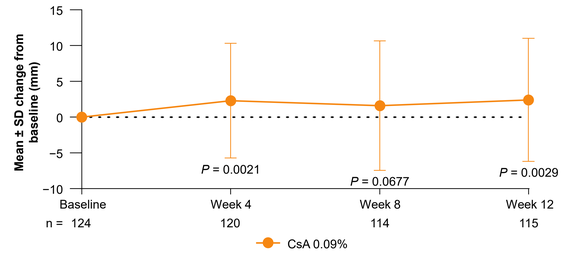


CsA 0.09%, cyclosporine ophthalmic solution 0.09%; SD, standard deviation.

Schirmer's test scores

- The mean ± SD baseline Schirmer's test score was 11.4 ± 8.2 mm
- Mean Schirmer's test score increased over time and the mean ± SD change from baseline at Week 12 was 2.4 ± 8.6 mm (*P* <0.01; **Figure 3**)
  - Mean changes from baseline in Schirmer's test score were also statistically significant at Week 4 (*P* <0.01)

Figure 3. Mean change from baseline in Schirmer's test scores

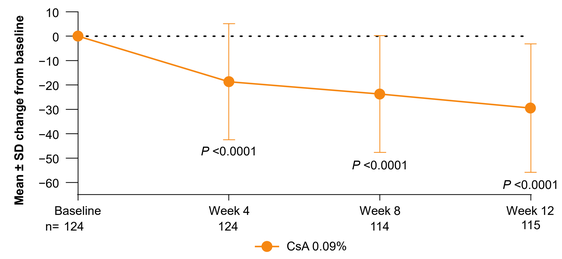


CsA 0.09%, cyclosporine ophthalmic solution 0.09%; SD, standard deviation.

Modified Symptom Assessment iN Dry Eye scores

- The mean ± SD baseline mSANDE global symptom score was 67.1 ± 21.1
- Mean mSANDE global symptom score decreased over time, and the mean ± SD change from baseline at Week 12 was −29.5 ± 26.4 (*P* <0.0001; **Figure 4**)
  - Mean changes from baseline in mSANDE global symptom score were also statistically significant at Weeks 4 and 8 (*P* <0.0001)

Figure 4. Mean change from baseline in modified Symptom Assessment iN Dry Eye scores

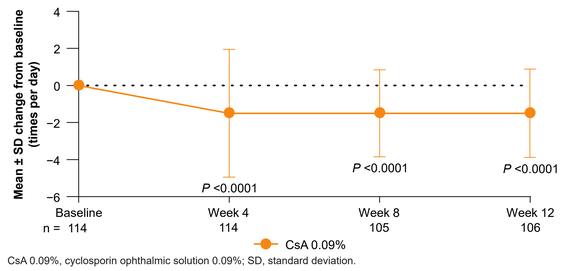


CsA 0.09%, cyclosporin ophthalmic solution 0.09%; SD, standard deviation.

Frequency of artificial tear use

- The mean ± SD baseline frequency of artificial tear use was 2.8 ± 4.0 times per day
- Mean frequency of artificial tear use decreased over time and the mean ± SD change from baseline at Week 12 was −1.5 ± 2.4 times per day (*P* <0.0001; **Figure 5**)
  - Mean changes from baseline in artificial tear use were also statistically significant at Weeks 4 and 8 (*P* <0.0001)

Figure 5. Mean change from baseline in frequency of artificial tear use



CsA 0.09%, cyclosporin ophthalmic solution 0.09%; SD, standard deviation.

Patient preference

- At the end of the 12-week study, 69.4% of patients preferred treatment with CsA 0.09% compared with 21.8% who preferred their previous treatment with CsA 0.05%

Safety

- CsA 0.09% was generally well tolerated, consistent with its established safety profile[6,7]
- In the safety population (N = 134), a total of 58 (43.3%) patients reported ≥1 treatment-emergent AE, most of which (73.8%) were mild in severity (**Table 2**)
- The most common treatment-related AEs were instillation site irritation (12.7%) and instillation site pain (2.2%); all other treatment-related AEs occurred in <2% of patients

Table 2. Overview of treatment-emergent adverse events

	All patients[a] N = 134
Total number of TEAEs	84
Mild, n (%)	62 (73.8)
Moderate, n (%)	18 (21.4)
Severe, n (%)	4 (4.8)
Treatment-related TEAEs, n (%)	36 (42.9)
TEAEs leading to study drug discontinuation, n (%)	11 (13.1)
Patients with ≥1 TEAE, n (%)	58 (43.3)
Patients with ≥1 serious TEAE, n (%)	2 (1.5)
Patients with ≥1 treatment-related TEAE, n (%)	26 (19.4)
Patients with TEAEs leading to study drug discontinuation, n (%)	9 (6.7)

[a]The safety population included all patients who received ≥1 dose of study medication.
TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Twice-daily CsA 0.09% elicited statistically significant improvements in central CFS, Schirmer's test, and mSANDE scores at Week 12 of treatment in patients with DED inadequately controlled on CsA 0.05%
- Patient-reported frequency of artificial tear use was significantly reduced at each time point after starting CsA 0.09%
- At the end of the study, 69.4% of patients preferred treatment with CsA 0.09% over their previous treatment with CsA 0.05%
- CsA 0.09% was generally well tolerated, with most reported AEs of mild severity

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ACKNOWLEDGMENTS

Medical writing and editorial assistance were provided by Ryan P Reynolds, PhD, of AlphaBioCom, a Red Nucleus company, under the direction of the authors; this support was funded by Sun Pharma.

DISCLOSURES

JJ reports consultant fees from Alcon, Aldeyra, Allergan, Amgen, Avellino, Azura, Bio-Tissue, Bruder, Dompe, Gaukos, Johnson & Johnson, Kala Pharmaceuticals, Novaliq, Ocuterra, Orasis, Oyster Point, Quidel, SeaGen, Sight Sciences, Sun Pharma, Tarsus, Thea, Trukera, Versea Biologics, Visus, and Zeiss; speaker fees from Allergan, Bio-Tissue, Gaukos, Kala Pharmaceuticals, Oyster Point, Quidel, Sight Sciences, and Sun Pharma; and research fees from Tarsus. He is also a shareholder for LacriSciences. **RA** reports consultant fees from Allergan, Lumenis, Sun Pharma, and Tarsus, and speaker fees from Allergan, Lumenis, Oyster Point, and Sun Pharma. **MH** reports nothing to disclose. **KKN** reports consultant fees from Abbvie, Alcon, Alderya, Azura, Bausch + Lomb, Bruder, Cavalry, Dompe, HanAll Bio, Harrow, Novartis, Shire, Nicox, Novaliq, Oyster Point Pharma, Palatin, Sydnexis, Tarsus, TearSolutions, Thea, Topcon, Trukera, Versea, Xequel and research fees from Aramis, Kowa, Science Based Health, Sylentis, and TearScience. **SCP** reports consulting fees from Dompe, Kala Pharmaceuticals, Kowa, and Senju; equity interest in Immuneyez and Unfold; and research funding from Dompe. **KT** reports consultant fees from Sun Pharma. **MU** and **BM** are employees of Sun Pharmaceutical Industries, Inc.