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ORIGINAL RESEARCH

# Real-World Effectiveness, Tolerability and Safety of Cyclosporine A 0.1% Cationic Emulsion in Severe Keratitis and Dry Eye Treatment

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## ABSTRACT

***Introduction***: The PERSPECTIVE study evaluated, in routine clinical practice, the effectiveness, tolerability and safety of cyclosporine A (CsA) 0.1% cationic emulsion (CE) in controlling severe keratitis in adults with dry eye who remained insufficiently controlled despite artificial tear (AT) use.

***Methods***: A prospective, multicenter, observational study was conducted at 44 ophthalmology clinics across Finland, Germany, Norway, Sweden and the UK. Adults treated with ATs for severe keratitis and dry eye received CsA 0.1% CE therapy (1 drop in both eyes at bedtime) and were followed up at weeks 4, 12 and 24 and at month 12. Primary endpoint was mean [standard deviation (SD)] change from baseline in corneal fluorescein staining (CFS; Oxford Grade Scale) at month 12 following CsA 0.1% CE initiation. Secondary endpoints examined ocular sign and symptom severity and adverse events (AEs).

***Results***: The full analysis set included 472 adults (75.9% female). Mean (SD) age was 61.9 (15.41) years. Mean (SD) CFS score was significantly reduced from baseline [2.56 (1.10)] at month 12 [1.10 (SD 1.13); $P < 0.0001$]. CFS score reductions were statistically significant from week 4, with further incremental decreases reported at study visits through month 12 ($P < 0.0001$). Severity of eyelid and conjunctival erythema was significantly reduced from baseline at week 4 and maintained through month 12 ($P < 0.001$). Tear film breakup time increased significantly from baseline at all study visits through month 12 ($P < 0.001$). Ocular symptom severity was significantly reduced from baseline at all study visits through month 12 ($P < 0.001$). Overall, 101 treatment-related AEs were reported. Most were mild/moderate (83.6%) and resolved by month 12 (73.3%).

The members of the PERSPECTIVE study group are listed in the Conclusion section of this article.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40123-022-00487-x.

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***Conclusions***: In routine clinical practice, CsA 0.1% CE provided statistically significant reductions in dry eye signs and symptoms. Improvements were seen at week 4 and maintained over 12 months. Treatment tolerability was good and consistent with previous CsA 0.1% CE clinical studies.
***Trial registration***: EU PAS register number: EUPAS 22376.

**Keywords:** Cyclosporine A 0.1% cationic emulsion; Dry eye disease; Real-world evidence; Severe keratitis

**Key Summary Points**

***Why carry out this study?***

Dry eye disease (DED) is a multifactorial and complex condition that may be challenging to diagnose and treat in clinical practice. It is an increasingly common condition requiring long-term treatment, which represents a significant burden for patients and is associated with reduced quality of life and productivity.

The PERSPECTIVE study aimed to expand the evidence base concerning the use of cyclosporine A (CsA) 0.1% cationic emulsion (CE) in controlling severe keratitis in adults with dry eye. The study examined, in a real-world clinical practice setting, the effectiveness, tolerability and safety of CsA 0.1% CE in adult patients with DED who had not improved despite treatment with tear substitutes.

***What was learned from the study?***

In routine clinical practice, CsA 0.1% CE provided significant improvements in dry eye signs and symptoms that were present from week 4 and maintained throughout the 12-month study period, and treatment was generally well tolerated

Ophthalmologists participating in the study typically selected patients with dry eye based on corneal fluorescein staining (CFS; Oxford Grade Scale: grade 0–V) scores of II and III for inclusion in the study. CFS was significantly reduced, compared with baseline score, at all study visits from week 4 through month 12.

The severity of key signs and symptoms of DED, including eyelid and conjunctival erythema, was significantly improved from baseline at all study visits through month 12, and adverse events were generally mild/moderate and resolved at the end of the study period.

## INTRODUCTION

Dry eye disease (DED), also known as keratoconjunctivitis sicca, is a chronic condition requiring long-term treatment. It is defined by the Tear Film Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II as a "multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" [1–7]. Two primary categories of DED have been defined: aqueous deficient and evaporative dry eye [1]. Meibomian gland dysfunction (MGD) is a key underlying cause of evaporative DED, while tear underproduction results in aqueous deficient dry eye [1]. However, most people with DED display signs and symptoms in varying combinations that relate to both types of disease [4]. Disruption of ocular surface homeostasis leads to the induction of pro-inflammatory pathways that cause ocular damage and neurosensory aberrations, resulting in a vicious circle of progressively worsening pathophysiology [1, 2, 3–7]. If left untreated, DED may progress in severity and result in permanent ocular damage [3, 7]. Symptoms include pain, ocular irritation and impaired/blurred vision as well as

stinging, burning or scratching sensations, all of which can limit performance of daily tasks and quality of life (QoL) [8].

DED is typically cyclical in nature with episodic worsening (or flares) of signs and symptoms occurring over time, including prolonged ocular inflammation (usually indicated by the presence of eyelid and/conjunctival hyperemia) and discomfort [9–11]. Topical and systemic medications, environmental or lifestyle factors (e.g. air conditioning, use of screen-based technologies) and allergies can exacerbate symptoms [9–14]. DED represents a significant QoL and economic burden due to loss of productivity and psychological issues (e.g. anxiety, depression), and individuals with specific character traits are at higher risk of developing the condition [12–17]. Absenteeism and presentism (attendance at work while unwell or unable to be productive) alone cost an estimated $11,302 per person with DED [13].

Treatment traditionally focuses on the control of symptoms and reduction of complications, with the aim of restoring ocular surface homeostasis and preventing further symptomatic flares [3]. Artificial tears (ATs) or tear substitutes offer protection and lubrication at the ocular surface, although treatment outcomes with ATs may be variable, and disease progression will invariably require the addition of topical anti-inflammatory treatments (e.g. corticosteroids, cyclosporine) to reduce inflammation and help to improve QoL [4, 6, 18–28]. The TFOS DEWS II and German Ophthalmology Society (DOG) guidelines and recent expert consensus recommendations advise that anti-inflammatory treatments should be used relatively early in the disease pathway (from stage 2), rather than being reserved for later stages of disease when the ocular surface may be less responsive to therapy [4, 29, 30]. Cyclosporine A (CsA) is a widely used anti-inflammatory treatment for DED that can be administered for long-term treatment of inflammation [4, 6, 18–29]. In contrast, corticosteroids are not recommended for long-term use due to a risk of ocular complications (e.g. ocular hypertension, cataracts and opportunistic infections) [4, 29]. Multicenter, randomized controlled trials (RCTs) have demonstrated efficacy and safety outcomes with CsA 0.05% anionic solutions or 0.1% cationic emulsion (CE) treatment, with significant improvement observed concerning the signs and symptoms of DED [20–24, 27]. In Europe, only CsA 0.1% CE is licensed for prescription and reimbursement [31]. It is approved for the treatment of severe keratitis in adult patients with DED that has not improved despite treatment with tear substitutes [31]. Two double-masked, randomized, parallel-group, vehicle-controlled phase III studies, SICCANOVE and SANSIKA, examined treatment outcomes with CsA 0.1% CE in people with moderate-to-severe and severe DED, respectively [21–24]. In both studies, CsA 0.1% CE was well tolerated, reduced corneal surface damage and lowered ocular surface inflammation [21–24]. Pooled analysis of SICCANOVE and SANSIKA outcomes confirmed that CsA 0.1% CE improved the signs and symptoms of DED, with a particular benefit to those with severe keratitis [20]. An open-label 24-month extension study also showed that the majority of people demonstrating improvement in DED signs and symptoms during the SANSIKA study did not relapse and sustained lower corneal fluorescein staining (CFS) scores after CsA treatment had been discontinued [24]. While CsA 0.1% CE has been shown to be generally well tolerated in clinical studies, some retrospective analysis and pre-clinical data indicate that tolerance may be reduced/low in certain populations (e.g. ocular graft vs. host disease), with pain/irritation at the site of installation being the main adverse event (AE) and reason for discontinuation reported [20–24, 28, 32–34].

Although RCTs are considered to be the gold standard approach for drug registration trials, strict inclusion and exclusion criteria mean that they are generally unable to accurately reflect the diverse patient population and situations typically encountered in clinical practice [35]. RCTs usually require wash-out periods when examining the effects of treatment switches, which are unlikely to be implemented in real-life clinical situations. Real-world evidence is becoming increasingly important and accepted by regulators (alongside conventional randomized trials) for demonstrating the effectiveness of treatments in routine practice [36–38]. These

data provide clinicians with an indication of the potential results they may observe in their own clinic as well as new insights concerning the treatment of disease and pharmacovigilance data [37].

Recently published real-world evidence indicates that patients with ocular surface inflammatory diseases (particularly those with dry eye) experience improved clinical outcomes with CsA 0.1% CE treatment, with reduced requirement for adjunctive steroids [25]. The aim of the present study was to expand the evidence base regarding the use of CsA 0.1% CE in routine clinical practice. The PERSPECTIVE study examined, in a real-world clinical setting, the effectiveness, tolerability and safety of CsA 0.1% CE in controlling severe keratitis in adult patients with dry eye who had not improved despite treatment with tear substitutes. Although the approved label for CsA 0.1% CE states that it should be used in the treatment of severe keratitis and dry eye, no formal threshold for CFS score (using the Oxford Grade Scale) is stipulated in the licensed indication, and the literature in this area does not clearly define the way in which disease severity should be graded [1–4, 29–31]. In routine clinical practice, ophthalmologists may evaluate the severity of keratitis and DED using a combination of CFS score, other signs (e.g. eyelid and/or conjunctival erythema), patient-reported symptoms and QoL factors [1, 4, 29–31]. This approach reflects the complex and multifactorial nature of the disease [1, 4, 29–31]. The PERSPECTIVE study therefore aimed to reflect real-world clinical practice and only specified that treatment should be prescribed in accordance with the approved label for CsA 0.1% CE based upon the judgment of the investigator. This approach was designed to gain insights regarding the typical profile (in terms of ocular signs and symptoms) and treatment outcomes for those patients considered by the treating physician to have disease of sufficient severity to warrant CsA 0.1% CE therapy. The study provides important insights concerning the treatment of keratitis and dry eye in ophthalmology clinics across Europe and the treatment outcomes that clinicians and their patients may expect.

# METHODS

The PERSPECTIVE study was a 12-month, European, non-interventional, multicenter, prospective cohort study. In line with European Medicines Agency (EMA) requirements, the trial was registered under the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) European Union electronic Register of Post-Authorization Studies (EU PAS Register) (EU PAS register number EUPAS 22376). The study complied with the principles of the Declaration of Helsinki of 1964 as revised in 2013. All subjects included were required to provide written informed consent prior to their enrollment. The protocol was approved by the institutional review board (IRB) or independent ethics committee (IEC) at each center/institution ahead of study initiation. The centers/institutions are listed alongside the relevant principal investigator in the PERSPECTIVE study group section at the end of this article.

Data were prospectively collected between 11 April 2017 and 14 November 2019 at 44 ophthalmology clinics based in Finland, Germany, Norway, Sweden and the UK. Study visits were conducted at baseline, weeks 4, 12, and 24 and month 12 following the initiation of CsA 0.1% CE. Baseline measures were recorded under topical AT treatment within 7 days prior to initiation of CsA 0.1% CE. Variables were documented for each eye separately at baseline and at subsequent study visits, with the eye demonstrating the highest CFS score (Oxford Grade Scale; grade 0–V) at baseline selected as the study eye. In cases where the CFS score was equal in both eyes at baseline, the right eye was selected as the study eye. As the study was conducted in a routine clinical practice setting, all study medications (CsA 0.1% CE, ATs or corticosteroids) were prescribed and reimbursed or paid for in accordance with local healthcare arrangements. No medication was supplied by the study sponsor.

## Study Population

Study investigators selected patients for inclusion according to the approved licensed

indication for CsA 0.1% CE. Male/female adults (aged > 18 years) with a diagnosis of DED and severe keratitis who were considered by the treating physician to have shown insufficient clinical improvement with their current AT treatment were included in the study. As the study was designed to capture real-world clinical practice, specific thresholds for CFS score or the severity of ocular signs/symptoms were not stipulated in the protocol for patient inclusion. Instead, patient selection was based upon the individual investigator's own clinical evaluation and opinion that the patient's medical history and their current ocular signs and symptoms were congruent with the licensed indication for CsA 0.1% CE and that they had demonstrated insufficient control with ATs. All participants were currently treated with tear substitutes. Subjects were excluded if they were previously or currently treated with CsA 0.1% CE, were taking immunosuppressants, had undergone ophthalmic surgery (within 6 months) or were pregnant, breastfeeding or planning a pregnancy.

### Study Treatment

Participants were instructed to administer CsA 0.1% CE (Santen Oy, Tampere, Finland), one drop daily in both eyes at bedtime, for 12 months. Concomitant use of dry eye therapies (steroid treatment and/or ATs) was allowed during the study. All treatments were recorded at baseline and at each study visit alongside the reasons for initiating CsA 0.1% CE therapy. Investigators were able to provide more than one reason for starting CsA 0.1% CE treatment, based on clinical assessment and the judgment of the investigator, which were selected from the following options: insufficient keratitis/DED control with prior medication; progression of keratitis/DED; poor local tolerance; poor compliance; other reasons.

### Efficacy Measures and Assessments

The primary endpoint was change in CFS score (Oxford Grade Scale) from baseline at month 12, following initiation of CsA 0.1% CE.

Secondary endpoints were change in CFS score from baseline at interim study visits, change in clinical signs and severity of symptoms from baseline and use of concomitant dry eye therapies. Clinical signs and symptoms were evaluated at each study visit and compared with baseline measures. Clinical signs comprised eyelid and conjunctival erythema severity, which were recorded using a 4-point scale (none, mild, moderate, severe), Schirmer's test (without anesthesia) and tear film breakup time (TBUT). Schirmer's test and TBUT assessments were optional at study visits. Ocular symptoms assessed during the study comprised foreign body sensation, burning/stinging, itching, pain, blurred vision, sticky feeling and photophobia. Symptom severity was recorded using a 4-point scale in each case (none, mild, moderate, severe). Visual acuity (VA) data were collected using either decimal, logMAR or fraction (foot or meters) scales. All values were converted into decimal scale for calculation purposes using appropriate conversion charts for analysis [39].

Investigators provided their evaluation of effectiveness and clinical signs with CsA 0.1% CE eyedrops compared with previous treatment using a 3-point scale (better, the same or worse). Patients and physicians reported their assessment of tolerability with the study medication using a 4-point scale (very good, good, satisfactory, poor). Reported AEs and treatment-related AEs were collected and documented at each visit and for the total study period.

### Statistical Analysis

ICON Plc (Dublin, Ireland) conducted all statistical analyses on behalf of the PERSPECTIVE study group. Results are presented for the full analysis set (FAS). Statistical analysis compared treatment outcomes at each study visit with baseline levels. The Bhapkar test was used to assess change in CFS at month 12 and interim visits as well as change in the severity of symptoms, eyelid erythema and conjunctival erythema. The Bhapkar test can be used in marginal homogeneity, and it assumes that the changes are non-directional [40]. A paired *t*-test or a Wilcoxon signed rank test was used to

assess the statistical significance of the change in CFS, VA, TBUT and Schirmer's test, compared with baseline.

## RESULTS

A total of 517 patients were screened, of whom 501 entered the study. Following exclusions due to protocol and prescribing deviations, 474 participants were treated with CsA 0.1% CE and 472 were included in the FAS (Fig. 1). Overall, 236 patients were included from Germany, 160 from the UK, 47 from Norway, 24 from Sweden and 5 from Finland. Participant demographics and characteristics at baseline are shown in Table 1. Mean [standard deviation (SD)] age was 61.9 (15.41; range 19.9–95.4) years and 75.9% were female. Associated systemic conditions included rheumatologic disease (13.8%) and primary Sjögren syndrome (8.9%). ATs were administered at least twice daily by 48.4% of participants. Among those included in the analysis, 12 (2.5%) patients were using a CE formulation of tear substitute (Cationorm®; Santen Oy) at baseline, which has a slightly different composition to the emulsion used in the CsA 0.1% CE study drug. Beyond those 12 individuals using a CE tear substitute formulation, patients used a range of preserved and preservative-free high- and low-viscosity aqueous or oil-based AT formulations in various combinations according to local country availability. The most frequent reason, as judged by the treating ophthalmologist, for initiating CsA 0.1% CE was insufficient keratitis/DED control with prior medication (79.9%) followed by progression of keratitis/DED (22.7%).

### Change in CFS from Baseline

At baseline, mean (SD) CFS score (Oxford Grade Scale) was 2.56 (1.10), with the most frequently reported CFS scores being grade II (33.0%) and grade III (32.6%). Twelve individuals included in the FAS had baseline CFS scores of 0, with 11 patients in this group having other moderate or severe clinical signs and/or symptoms and one patient having mild conjunctival and eyelid erythema as well as foreign body sensation.

Figure 2a shows the change in mean CFS score from baseline at each study visit. Mean (SD) CFS score at month 12 was 1.10 (1.13), representing a statistically significant mean (SD) change from baseline of 1.42 (1.16; $P < 0.0001$). At month 12, 77.5% demonstrated a reduction in CFS score from baseline, while 19.6% showed no change and 2.9%

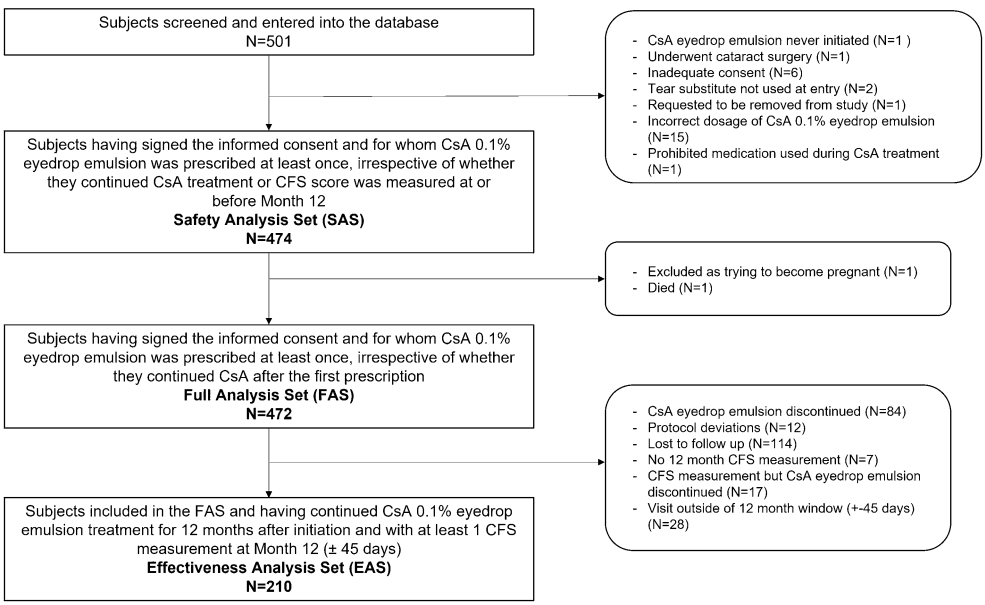


**Fig. 1** Flow chart of patient disposition. *CE* Cationic emulsion, *CFS* corneal fluorescein staining, *CsA* cyclosporine A

**Table 1** Demographics and characteristics of participants

| Participant demographics and characteristics | Values |
|---|---|
| Sex, *n* (%) | |
| Males | 114 (24.2) |
| Females | 358 (75.9) |
| Age (years) | |
| Mean (SD) | 61.9 (15.41) |
| Range | 19.9–95.4 |
| Study eye (worst CFS at baseline), *n* (%) | |
| Left | 91 (19.3) |
| Right | 381 (80.7) |
| Ongoing associated systemic disease, *n* (%) | |
| Diabetes | 33 (7.0) |
| Rheumatologic diseases | 65 (13.8) |
| Primary Sjögren's syndrome | 42 (8.9) |
| Secondary Sjögren's syndrome | 16 (3.4) |
| Other[a] | 230 (48.7) |
| - Hypertension | 67 (29.1) |
| - Thyroid disorders | 55 (23.9) |
| - Hypercholesterolemia | 29 (12.6) |
| - Allergy | 16 (7.0) |
| - Asthma | 15 (6.5) |
| Concomitant DED medications at Baseline, n (%) | |
| Initiated steroids at Baseline in addition to CsA 0.1% CE | 35 (7.4) |
| Prior steroid users expected to continue their use in addition to CsA 0.1% CE | 40 (8.5) |
| Artificial tear use[b] | |
| 6 times per day | 60 (6.9) |
| 5 times per day | 83 (9.5) |
| 4 times per day | 108 (12.4) |
| 3 times per day | 107 (12.3) |
| Twice per day | 63 (7.2) |
| Daily/once | 204 (23.4) |
| As needed | 123 (14.1) |
| VA decimal score, mean (SD) (*n* = 454) | 0.65 (0.36) |
| Schirmer's test (mm), mean (SD) (*n* = 172) | 9.91 (9.67) |
| TBUT (seconds), mean (SD) (*n* = 350) | 4.25 (2.97) |
| CFS score (Oxford Grade Scale) | |
| 0 | 12 (2.6) |
| I | 62 (13.2) |
| II | 155 (33.0) |
| III | 153 (32.6) |
| IV | 67 (14.3) |
| V | 20 (4.3) |
| Mean (SD) CFS score (*n* = 469) | 2.56 (1.10) |

*CFS* Corneal fluorescein staining, *DED* dry eye disease, *IQR* interquartile range, *SD* standard deviation, *TBUT* tear film breakup time, *VA* visual acuity

[a]The denominator used for percentage calculations was the number of patients with other diseases

[b]In cases where patients were using multiple artificial tear treatments at the same time, the dose frequency of each was reported separately

demonstrated an increase in CFS. Overall, at month 12, 77.5% showed reductions in CFS score compared to baseline level of ≥ 1 grade, 47.5% demonstrated reductions of ≥ 2 grades and 16.7% demonstrated reductions of ≥ 3 grades. The change in CFS score was statistically significant compared with baseline at each study visit ($P < 0.0001$). Mean (SD) CFS scores at weeks 4, 12 and 24 were 1.77 (1.22), 1.46 (1.17) and 1.24 (1.23), respectively, with the corresponding reductions from baseline being 0.84 (0.97), 1.09 (1.04) and 1.39 (1.17) ($P < 0.0001$). Figure 2b shows the distribution of CFS score reported at each study visit.

## Clinical Signs and Ocular Symptoms

The change in the severity of eyelid erythema from baseline was statistically significant from

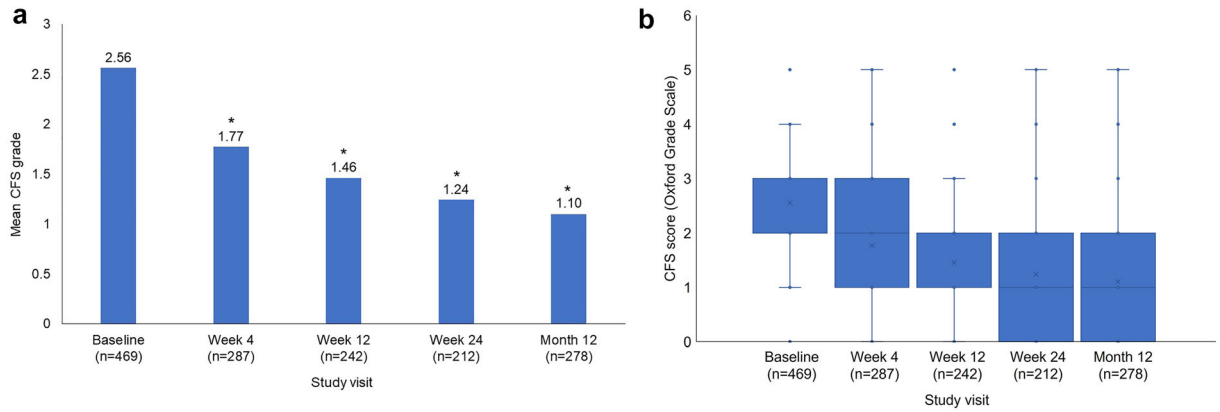


**Fig. 2** **a** Change in mean CFS score from baseline following initiation CsA 0.1% cationic emulsion (FAS). *Indicates that the change in mean CFS score from baseline was statistically significant at week 4, week 12, week 24 and month 12 ($P < 0.0001$). A two-sided test (Wilcoxon sign-rank test) was used to test significance. **b** Boxplot of distribution of CFS score reported at each study visit (FAS). In the FAS, CFS grade data were available for 469 patients at baseline, 287 at week 4, 242 at week 12, 212 at week 24 and 278 at month 12. *CFS* corneal fluorescein staining, *FAS* Full analysis set

week 4 and at all study visits through month 12 ($P < 0.001$). Moderate-to-severe eyelid erythema was reported in 30.8% of participants at baseline and in 9.2% at month 12 ($P < 0.001$). At the end of the study period, 67.7% of patients no longer had eyelid erythema of any severity. Change in conjunctival erythema severity was also statistically significant from baseline when assessed at week 4 and at all study visits through month 12 ($P < 0.001$). Moderate-to-severe conjunctival erythema was observed in 28.3% at baseline and in 9.0% at month 12 ($P < 0.001$). At the end of the study, conjunctival erythema was reported to be absent in 58.8% of patients.

Change in Schirmer's test result from baseline was not significant at month 12 ($P = 0.113$). Increases in TBUT, versus baseline, were statistically significant and incrementally increased at all study visits from week 4 through month 12 ($P < 0.001$). At month 12, mean (SD) TBUT had increased from 4.25 (SD 2.97) seconds (s) at baseline to 5.69 (3.61) s, providing an increase of 1.78 (3.89) s ($P < 0.001$).

Severity of all symptoms examined was significantly reduced at each study visit from week 4 ($P < 0.001$). Patients demonstrated significant reductions in the severity of foreign body sensation, burning/stinging, itching, eye pain, blurred vision and photophobia from week 4, and these reductions were sustained through month 12 ($P < 0.001$). The majority of patients reported ocular symptoms to be improved or stabilized at month 12 (Fig. 3), compared with baseline, regarding foreign body sensation (88.2%), burning/stinging (83.1%), itching (90.6%), eye pain (91.9%), sticky feeling (90.9%), blurred vision (88.9%) and photophobia (84.7%). Statistically significant increases in VA score were seen from week 12 through month 12 ($P \leq 0.0064$). Mean (SD) VA decimal score was 0.65 (0.36) at baseline and 0.73 (0.38) at month 12, representing an increase of 0.06 (SD 0.33; $P = 0.0064$).

Of those 12 participants with CFS scores of 0 at baseline, eight had recorded information regarding ocular signs and symptoms at month 12. Among five of these patients, signs and/or symptoms were generally reduced in severity at month 12, compared with baseline, while two patients experienced no change from baseline and one participant reported varied results (Fig. 4).

## Physician and Patient Assessments

Physicians considered CsA 0.1% CE to be more effective than previous medications in 73.6% of cases and equal to prior treatment in 23.4% at

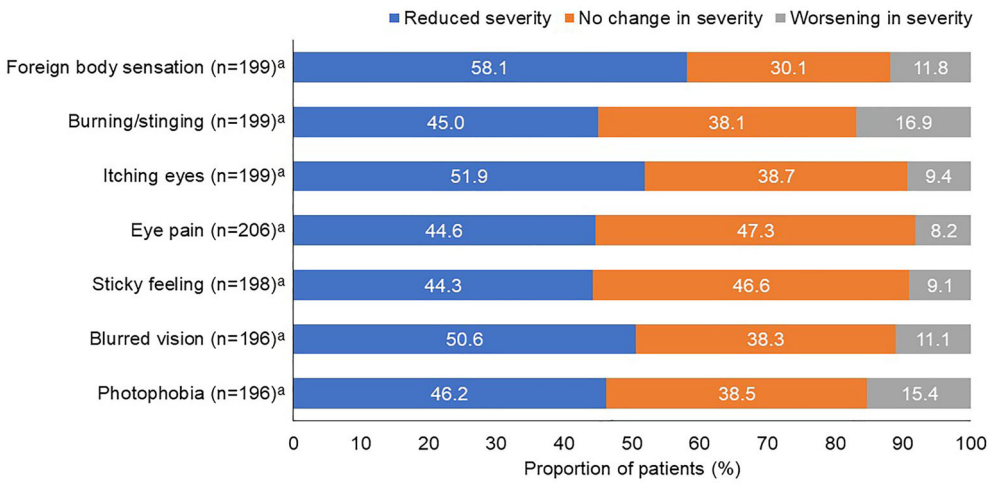


**Fig. 3** Change from baseline in severity of symptoms at month 12 following initiation of CsA 0.1% cationic emulsion (FAS). [a]Number of patients in the FAS with subjective symptom data available/reported at month 12

month 12. At month 12, clinical signs, as assessed by the physician, were reported to be reduced compared with prior medication in 71.7% of cases and the same as previous medication in 25.2%. Overall, 77.0% of patients and 80.4% of physicians reported tolerability with CsA 0.1% CE to be good or very good at month 12.

### Discontinuation from Study Treatment

Physicians reported different reasons for ceasing CsA 0.1% CE treatment. In total, 84 participants (17.8%) discontinued CsA 0.1% CE treatment during the study period. Of these patients, discontinuations were due to poor local tolerance with CsA 0.1% CE (36.9%), insufficient keratitis or DED control (9.5%), AEs (7.1%), poor compliance (3.6%) and personal/other reasons (51.2%). No discontinuations were due to progression of DED or keratitis during the study period.

### Safety Assessments

Overall, 280 AEs were reported during the study period. The majority were non-serious (88.6%) and mild or moderate in severity (83.6%), and this was the case regardless of the CFS score recorded at baseline. In total, 101 (36.1%) AEs were considered to be treatment-related, two of which were serious (back pain and thyroid disorder; Table 2). By the end of the study period, most treatment-related AEs (73.3%) were resolved or were resolving (including the 2 serious AEs), 17.8% had not yet resolved and the status of the remaining 8.9% was not reported.

## DISCUSSION

This prospective observational study examined the effectiveness, tolerability and safety of CsA 0.1% CE treatment in a real-world setting. The inclusion and exclusion criteria reflected the patient group defined in the approved CsA 0.1% CE label. The study reaffirms the findings of randomized trials examining the use of CsA 0.1% CE in the treatment of DED, demonstrating statistically and clinically significant improvements in the ocular signs and symptoms of dry eye and keratitis [20–24]. In contrast with conventional RCTs, participants were not required to undergo a wash-out period before starting the study medication, and concomitant therapy with steroids and ATs was allowed to continue following initiation of CsA 0.1% CE treatment. The study therefore reflects current clinical practice and provides information on circumstances under which CsA is prescribed and the efficacy and tolerability outcomes that

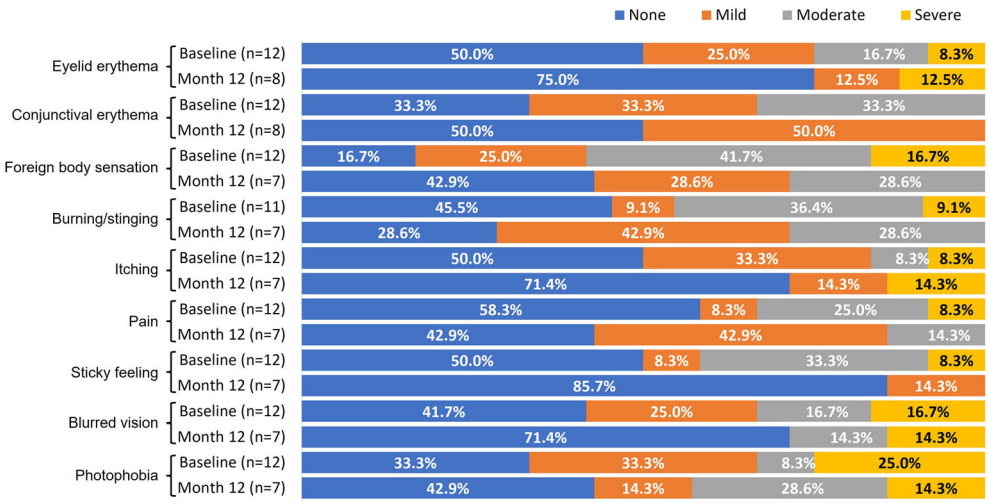


**Fig. 4** Severity of eyelid and conjunctival hyperemia and ocular symptoms at baseline and month 12 for patients with a CFS score of 0 at baseline

may be observed in routine ophthalmology practice, where patients are prescribed multiple concomitant therapies and may, in addition, use over-the-counter products.

Mean CFS score was significantly reduced during the follow-up period, with patients experiencing significant reductions from week 4 that were sustained and incrementally improved during the 12-month study ($P < 0.0001$). At month 12, most patients (77.5%) demonstrated reductions in CFS score from baseline of $\geq$ 1 grade, almost half (47.5%) had reduced their CFS score by at least 2 grades and 16.7% by $\geq$ 3 grades with CsA 0.1% CE treatment. Given the study design, this is probably indicative of routine clinical practice and suggests that the majority of patients treated with CsA 0.1% CE may maintain ocular surface improvements over a prolonged period. Previous studies have shown that efficacy may be sustained following discontinuation from CsA 0.1% CE and that those treated for 12 months were least likely to relapse [24].

CFS score at baseline was typically graded at II or III, suggesting that ophthalmologists select patients for topical CsA 0.1% CE therapy at an earlier disease stage compared with the inclusion criteria generally used in randomized studies (CFS IV or V) [20, 22, 23]. However, no formal thresholds have been defined regarding DED severity in relation to CFS score, and the patient's perception of symptom severity might influence the grade of disease attributed by the diagnosing physician as the burden of DED directly relates to the symptoms experienced by the patient [1, 3]. Further examination of data for the 12 patients with baseline CFS grade 0 revealed that the majority (11 of the 12) of these individuals had some moderate or severe clinical signs and/or symptoms prior to initiating CsA 0.1% CE, which were likely to have impacted their QoL and may have provided a signal to the clinician that, in their clinical opinion, the patient could benefit from CsA therapy. Where data were available, the majority of these participants reported improvements in the severity of signs and symptoms at month 12. It is well established that a proportion of patients with dry eye seen by ophthalmologists in clinical practice will exhibit conflicting signs and symptoms, and this seems congruent with the population observed in the PERSPECTIVE study [4]. Additional subanalysis to examine the change in ocular signs and symptoms in patients reported to have baseline CFS scores of between I and II and III and IV would be of value to provide further data regarding the key signs/symptoms that may have prompted decisions to initiate CsA 0.1% CE therapy and the treatment outcomes achieved in each of these

**Table 2** Treatment-related adverse events reported during the study period

| System/organ class | Number of treatment-related AEs | System/organ class | Number of treatment-related AEs |
|---|---|---|---|
| Ocular | | Musculoskeletal | |
| Eye irritation | 30 | Backpain | 1 |
| Eye pain | 14 | Dermatological | |
| Ocular hyperemia | 5 | Acne | 1 |
| Conjunctivitis | 3 | Dermatitis | 1 |
| Dry eye | 3 | Rash | 1 |
| Vision blurred | 3 | Skin discoloration | 1 |
| Cataract | 2 | Skin ulcer | 1 |
| Eye allergy | 2 | Endocrine | |
| Eye discharge | 2 | Thyroid disorder | 1 |
| Eye pruritus | 2 | Gastrointestinal | |
| Eyelid oedema | 2 | Nausea | 2 |
| Lacrimation increased | 2 | Neurological | |
| Ocular discomfort | 2 | Dizziness | 1 |
| Blepharitis | 1 | Headache | 2 |
| Conjunctival hemorrhage | 1 | Pain | 1 |
| Conjunctival hyperemia | 1 | Respiratory | |
| Conjunctival edema | 1 | Epistaxis | 1 |
| Conjunctivitis allergic | 1 | Nasal congestion | 1 |
| Corneal infiltrates | 1 | Nasal inflammation | 1 |
| Eczema eyelids | 1 | Immune disorders | |
| Eyelid margin crusting | 1 | Drug hypersensitivity | 1 |
| Eyelid pruritus | 1 | Swelling face | 1 |
| Ocular icterus | 1 | | |
| Photophobia | 1 | | |

*AEs* Adverse events

subgroups. Indeed, moving forward, the authors plan to conduct further CFS subgroup analysis of the PERSPECTIVE data. The PERSPECTIVE study highlights the considerable variation in clinical opinion across the ophthalmology community regarding the factors that indicate the presence of severe keratitis and DED, and further studies and/or clinical guidelines would be valuable in providing ophthalmologists with greater clarity regarding the diagnostic criteria that should be used to grade the severity of DED and to support the daily management of this common, complex and multifactorial condition.

Each of the symptoms examined were significantly improved from week 4 following initiation of CsA 0.1% CE and at all subsequent study visits. More than 83% of patients reported symptoms to be improved or stabilized at month 12, which is consistent with recent real-world data regarding the use of CsA 0.1% CE in DED [24]. Statistically significant reductions in the severity of eyelid erythema and conjunctival erythema were shown at all study visits, while increases in VA and TBUT scores were also statistically significant.

The safety and tolerability profile of CsA 0.1% CE was consistent with previously published studies in this area [20–25]. Patient evaluation of tolerability indicated a high level of satisfaction throughout the 12-month treatment period. In addition, most treatment-related AEs were mild or moderate in severity and were resolved or resolving by the end of the study. Treatment-related AEs occurred in 36.1% of patients, which is similar to that reported in the pooled analysis for the SANSIKA and SICCANOVE studies (35.1%) [20]. Eye pain and irritation were the most frequently reported treatment-related AEs in the current study, and this is also true for previously published randomized trials [20–24, 27]. While previous studies highlight that some populations may experience tolerability issues (particularly discomfort/pain at the site of instillation), just 31 participants (6.6% of the FAS) withdrew from the PERSPECTIVE study due to poor local tolerance, which was also slightly lower than the proportion withdrawing due to ocular treatment-related AEs in the SANISKA/SICCANOVE pooled analysis (9.3%) [20, 32–34].

While the real-world setting of the current study provides important insights regarding the outcomes that may be achieved in routine practice, there are a number of limitations that may be associated with the observational study's design. Patients were allowed to enter the study if judged by the investigating clinician to have severe keratitis and DED, based upon a combination of factors that included ocular signs and symptoms and the impact of disease on QoL. This resulted in the inclusion of a heterogenous study population, which is reflective of routine clinical practice but may present challenges when comparing treatment outcomes against those from randomized trials examining CsA 0.1% CE use in a homogenous and stringently selected group [21–24]. Nonetheless, as demonstrated in previously published retrospective and observational analyses, real-world studies enable factors such as treatment tolerance to be examined at a practical level to improve understanding regarding those patients who may be best suited to CsA 0.1% CE therapy as well as those who would benefit from a different approach [25, 32, 34]. In accordance with usual clinical practice in the real-world setting, patients were allowed to continue AT therapy throughout the study, which could have contributed to the healing of the corneal surface and the therapeutic effect observed with CsA 0.1% CE treatment. However, patients entering the study were considered to have insufficient keratitis/DED control or progression of disease according to clinical assessment by the treating physician. Around one-third were also reported to have moderate-to-severe eyelid (30.8%) or conjunctival (28.3%) erythema at baseline, denoting the presence of inflammation [3, 29]. While ATs may help in providing lubrication at the ocular surface, data are inconsistent regarding the treatment outcomes seen with ATs in DED. ATs do not address the inflammatory pathways and subsequent ocular surface aberrations that drive the vicious circle of DED and progressive disease [29]. The TFOS DEWS II recommendations, German Ophthalmology Society (DOG) guidelines and a recent clinical consensus paper have noted the anti-inflammatory and immunomodulatory effects of CsA treatment and recommended that such therapies should be used in conjunction with tear substitutes when conjunctival or eyelid hyperemia are present and when AT therapy alone no longer provides adequate control [3, 4, 29, 30]. DED therapy should aim to restore ocular surface homeostasis and to reduce the frequency and severity of symptomatic flares [4, 29]. As a multifactorial condition, management strategies usually require more than one type of therapy to target specific underlying pathophysiological aspects of disease or to provide symptomatic relief [4, 29]. The PERSPECTIVE study design aimed to reflect this real-

world approach to therapy and to report the outcomes expected when CsA 0.1% CE is used in clinical practice. Patients entering the study were allowed to use ATs of all types, but only 12 of the 472 patients included in the FAS used a CE formulation of tear substitute. In addition to the proven anti-inflammatory action of cyclosporine, it is likely that the formulation of the CsA 0.1% CE therapy used in the study may have provided further benefits regarding ocular surface health, and subjective symptoms as CE ATs have previously been shown to improve the signs and symptoms of dry eye in people with mild-to-moderate disease [20–25, 27, 41].

A significant proportion of the FAS population discontinued study medication before the end of the 12-month treatment period without informing the investigator (as highlighted in Fig. 1). In contrast to traditional RCTs, patients were not mandated to continue treatment until month 12 and may have chosen to stop their CsA therapy for any number of unreported reasons. Without further investigation, it is not possible to understand which proportion of discontinuations were due to lack of efficacy or to patients simply considering their symptoms to have been reduced sufficiently that they no longer regarded treatment to be necessary. Since DED is known to be cyclical in nature and symptoms are associated with ocular inflammation, patients may have suspended treatment once they had achieved symptomatic relief and believed their condition to be well controlled [9–11]. Previous CsA 0.1% CE studies have demonstrated significant improvements after 6 months of treatment, and the drop-out rate later in the study may be reflective of this [22, 23].

## CONCLUSION

DED is a chronic disease requiring long-term treatment, and CsA 0.1% CE provided significant improvements in the severity of its signs and symptoms, which were evident from week 4 and sustained over 1 year of treatment. CsA 0.1% CE was generally well-tolerated. This large, multicenter, observational study provides insights from real-world settings regarding the treatment of dry eye and keratitis across Europe and the outcomes that ophthalmologists and their patients may expect with CsA 0.1% CE.

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***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.



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