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Efficacy and safety of 0.1% ciclosporin A cationic emulsion in dry eye disease: a pooled analysis of two double-masked, randomised, vehicle-controlled phase III clinical studies

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ABSTRACT

Background/aim To assess the treatment effect of 0.1% ciclosporin A cationic emulsion (CsA CE) versus vehicle on signs/symptoms of dry eye disease (DED) in various subgroups (moderate-to-severe DED/severe DED/Sjögren's syndrome (SS)/SS with severe DED).

Methods Pooled data were analysed from two similar phase III studies: SICCANOVE (moderate-to-severe DED) and SANSIKA (severe DED with severe keratitis). In both studies, patients aged ≥18 years received CsA CE 0.1% (n=395) or vehicle (n=339) once daily for 6 months. A composite responder efficacy endpoint (corneal fluorescein staining–Ocular Surface Disease Index (CFS–OSDI) at month 6) was used to evaluate the efficacy of CsA CE in alleviating signs/symptoms of DED (response defined as improvement of ≥2 grades in CFS and ≥30% in OSDI (baseline to month 6)). Human leucocyte antigen-DR (HLA-DR) conjunctival expression was used as a biomarker of ocular surface inflammation.

Results CsA CE–treated patients were significantly more likely to be CFS–OSDI responders than vehicle-treated patients in the overall (OR 1.66, 95% CI 1.11 to 2.50; P=0.015), severe DED (1.80, 1.04 to 3.19; P=0.038) and SS with severe DED (3.37, 1.20 to 11.19; P=0.030) populations. The difference was not significant for CsA CE versus vehicle for the overall Sjögren's population (OR 1.77, CI 0.89 to 3.66; P=0.109). CsA CE also significantly reduced median HLA-DR expression versus vehicle at 6 months (P=0.002).

Conclusion Pooled phase III data indicate CsA CE produced significant improvement in signs/symptoms versus vehicle in patients with moderate-to-severe DED (especially in those with severe keratitis), including patients with SS with severe DED.

INTRODUCTION

The Dry Eye Workshop II has recently proposed a new definition of dry eye disease (DED): DED is a multifactorial disease of the ocular surface characterised 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 aetiological roles.[1] DED affects 5%–50% of the population according to worldwide surveys,[2] and patients can experience debilitating effects, both physically and psychologically, from ocular pain and irritative symptoms; difficulties performing basic activities of daily living such as driving and using a computer; and visual problems such as blurry vision.[2 3] Management of DED is complicated by the fact that it is driven by a self-perpetuating vicious cycle of tear film instability, hyperosmolarity and ocular surface inflammation.[4 5] Without treatment, DED can progress and increase in severity, becoming more refractory to treatment and potentially leading to permanent ocular damage.[4 6]

Current treatment strategies typically rely on the use of artificial tears to lubricate and hydrate the ocular surface, but this approach provides only short-term symptomatic relief that does not address ocular surface inflammation, the principal underlying pathophysiological component of chronic DED.[7 8] Ciclosporin A (CsA), an anti-inflammatory agent, has shown significant benefits in moderate-to-severe DED and has been the focus of increasing interest and investigation in recent years.[9] When applied topically as an oil-based formulation, CsA has low bioavailability and is poorly tolerated[10]; however, in 2015, a cationic emulsion (CE) formulation containing 0.1% (1 mg/mL) CsA (CsA CE; Ikervis; Santen SAS, Evry, France) was approved by the European Medicines Agency for the treatment of severe keratitis in adults with DED that has not improved despite treatment with tear substitutes. Compared with previously available formulations of CsA, CsA CE has a prolonged precorneal residence time and improved bioavailability, allowing for once-daily instillation.[11–14] The efficacy and safety of CsA CE were assessed in two double-masked, randomised, parallel-group, vehicle-controlled phase III studies: SICCANOVE, in patients with moderate-to-severe DED; and SANSIKA, in patients with severe DED. Overall, CsA CE was well tolerated and efficacious in reducing corneal surface damage and ocular surface inflammation in patients with moderate-to-severe DED.[15–17]

Pooled data from the SICCANOVE and SANSIKA studies were analysed to better understand the magnitude of the treatment effect of CsA CE, compared with vehicle, on signs and symptoms

of DED in the overall DED population and in multiple patient subgroups defined by age, sex, menopausal status, disease severity or duration and the presence or absence of Sjögren's syndrome (SS).

METHODS

Study design and participants

Data for this pooled analysis were obtained from two randomised, 6-month phase III clinical studies (EudraCT numbers: 2007-000029-23 (SICCANOVE), 2011-000160-97 (SANSIKA)) that evaluated the efficacy and safety of CsA CE in patients with moderate-to-severe DED.[15 16] Both studies were conducted in accordance with the principles of Good Clinical Practice and with the ethical principles set out in the Declaration of Helsinki. All enrolled patients provided written informed consent. Efficacy and safety methods and results from each study have been previously described[15 16]; the design of both studies is outlined in online supplementary figure 1 and briefly described below.

The SICCANOVE and SANSIKA studies were similar in design, allowing the data to be pooled for analysis. Both were multicentre, double-masked, parallel-group, controlled studies conducted in Europe in which patients ≥18 years of age with DED were randomised to receive once-daily CsA CE 0.1% (1 mg/mL) or its vehicle for 6 months. The SICCANOVE study included patients with moderate-to-severe DED (in the same eye: ≥1 symptom of ocular discomfort with a severity score ≥2 (on a 4-point scale), tear breakup time ≤8 s, corneal fluorescein staining (CFS) score between 2 and 4 (modified Oxford scale; 0 to 5), Schirmer test without anaesthesia ≥2 mm/5 min and <10 mm/5 min, and corneal/conjunctival lissamine green staining score ≥4 (van Bijsterveld scale)).[16] The SANSIKA study enrolled patients with severe DED (CFS=4 (modified Oxford scale; 0 to 5), Schirmer test without anaesthesia ≥2 mm/5 min and <10 mm/5 min, and Ocular Surface Disease Index (OSDI) score ≥23).[15] All patients who received active treatment or vehicle in the SICCANOVE and SANSIKA studies were included in the pooled analysis.

Study assessments and endpoints

Both studies included objective assessments of DED signs, such as CFS score and Schirmer test, as well as subjective assessments of DED symptoms, such as OSDI and visual analogue scales, which assessed patient symptoms (burning or stinging, foreign body sensation, itching, eye dryness, pain, blurred vision, sticky feeling and photophobia). Efficacy was determined only in the analysis eye, defined as the worst eye meeting the entry criteria listed above. The primary efficacy endpoint in the pooled analysis was a composite responder efficacy endpoint (CFS–OSDI) at month 6, defined as an improvement in both CFS (modified Oxford scale) by ≥2 grades from baseline and OSDI score by ≥30%. Human leucocyte antigen-DR (HLA-DR) expression on conjunctival epithelial cells (as assessed by impression cytology) at baseline and at month 6 was evaluated to investigate the relationship between disease severity (CFS score) and ocular surface inflammation.

Ocular and systemic adverse events were monitored throughout the SICCANOVE and SANSIKA studies (baseline visit through month 6 visit). Other safety assessments included best-corrected distance visual acuity (BCDVA), intraocular pressure (IOP) and blood sampling of systemic CsA levels.

Table 1 Demographic and baseline characteristics of patients included in the pooled full analysis set

	CsA CE (n=395)	Vehicle (n=339)
SANSIKA study (n, %)	154 (39.0)	91 (26.8)
SICCANOVE study (n, %)	241 (61.0)	248 (73.2)
Mean age, years (SD)	58.7 (13.2)	59.5 (12.5)
Female, n (%)	331 (83.8)	291 (85.8)
Sjögren's syndrome, n (%)	147 (37.2)	122 (36.0)
Severe DED, n (%) (CFS grade 4, OSDI ≥23)	193 (48.9)	126 (37.2)
HLA-DR data available, n (%)	94 (23.8)	74 (21.8)
CFS, mean (SD)—SANSIKA study	4.00 (0.00) (n=154)	4.00 (0.00) (n=90)
CFS, mean (SD)—SICCANOVE study	2.83 (0.71) (n=241)	2.80 (0.72) (n=248)
OSDI, mean (SD)—SANSIKA study	61.4 (19.4) (n=154)	58.8 (18.4) (n=91)
OSDI, mean (SD)—SICCANOVE study	44.41 (21.94) (n=241)	41.96 (21.84) (n=248)

CFS, corneal fluorescein staining; CsA CE, 0.1% (1 mg/mL) ciclosporin A cationic emulsion; DED, dry eye disease; HLA-DR, human leucocyte antigen-DR; OSDI, Ocular Surface Disease Index.

Statistical analyses

CFS–OSDI responder rates were analysed with a logistic regression model (with 'treatment' and 'pooled country' as factors) using imputed data. Study effect was included as a fixed effect to account for the structure of the data set. The CFS–OSDI responder rate was analysed in four patient populations: (1) all DED patients (full analysis set (FAS); n=734), (2) severe DED (n=319; patients with CFS grade 4 and OSDI ≥23), (3) all SS patients (n=269; patients with SS) and (4) SS/severe DED (n=130; patients with SS and severe DED). Sensitivity analyses for CFS–OSDI responder rates were performed using the main logistic model on the per-protocol set, on the FAS (observed data) and on the FAS by treatment received. Sensitivity analyses were also performed using the Cochran-Mantel-Haenszel test and controlling for pooled country.

CFS measurements (changes from baseline to month 6) were analysed by age, sex, menopausal status, SS status and disease duration in a subset of patients (n=629) who had CFS values at baseline and at month 6. The model was adjusted for treatment, study, visit and treatment by study. HLA-DR data were analysed after logarithmic transformation using an analysis of covariance model with 'treatment' and 'pooled country' as fixed factors and baseline score as a covariate. Because the data distribution for HLA-DR expression was found to be log-normal, median, rather than mean, values were reported as a measure of location.

RESULTS

Study population

The pooled FAS (all DED patients) population included 734 patients (table 1), 395 CsA CE patients and 339 vehicle patients. Most of the patients (84.7%) were women, 43.5% had severe DED and 36.6% had SS. Overall, demographic and baseline disease characteristics were well balanced across treatment groups.

Co-responder analysis

Patients treated with CsA CE were more likely to be CFS–OSDI responders than patients treated with vehicle (figure 1). In the FAS (all DED patients) population, 21.6% of CsA CE

Fig. 1

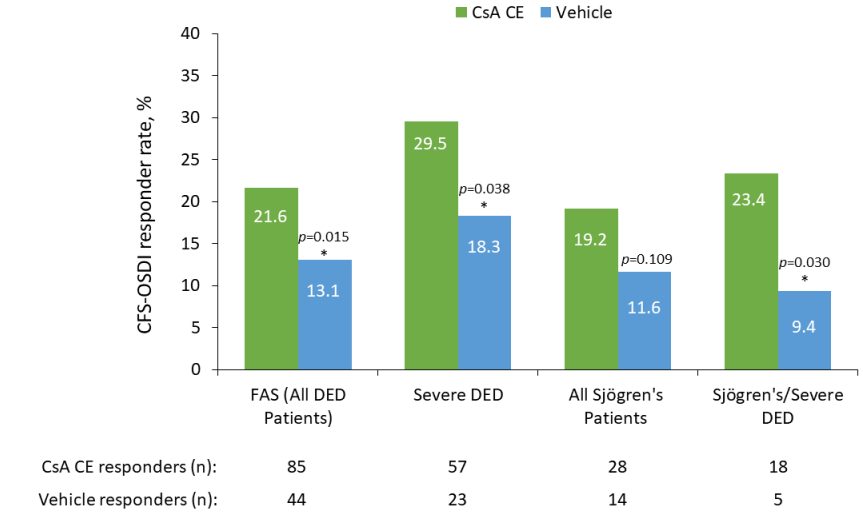

Figure 1 CFS–OSDI responder rates in the pooled analysis. *Statistically significant difference for CsA CE versus vehicle (P<0.05). Values represent imputed data. The P values were calculated using a logistic regression model. CFS, corneal fluorescein staining; CsA CE, 0.1% (1 mg/mL) ciclosporin A in a cationic emulsion; DED, dry eye disease; FAS, full analysis set; OSDI, Ocular Surface Disease Index.

patients achieved a CFS–OSDI response, compared with 13.1% of patients treated with vehicle (P=0.015). In the subgroup of patients with severe DED at baseline, 29.5% of patients with CsA CE achieved a CFS–OSDI response, compared with 18.3% of vehicle patients (P=0.038). In the overall SS group, differences were not statistically significant: 19.2% of CsA CE patients achieved a CFS–OSDI response, compared with 11.6% of vehicle patients (P=0.109). However, statistical significance was reached in the subgroup of patients with SS with severe DED (23.4% for CsA CE patients vs 9.4% for vehicle patients; P=0.030).

The ORs for CFS–OSDI response for the individual and combined studies illustrate the same trends, favouring CsA CE treatment over vehicle except in the overall SS

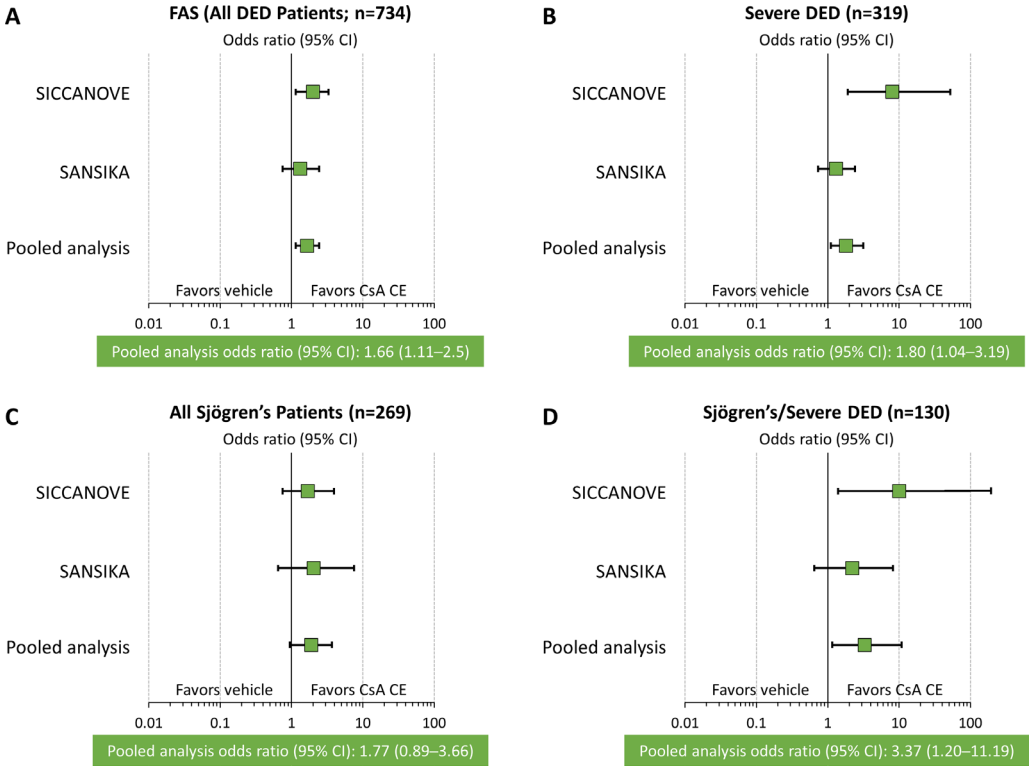

Figure 2 Pooled analysis and individual study results for the effect of CsA CE in improving both signs and symptoms (assessed by CFS–OSDI responder rate) in (A) all patients, (B) patients with severe DED, (C) all patients with SS and (D) patients with SS and severe DED at baseline. A response was defined as improvement of ≥2 grades in CFS and ≥30% in OSDI. CFS, corneal fluorescein staining; CsA CE, 0.1% (1 mg/mL) ciclosporin A in a cationic emulsion; DED, dry eye disease; FAS, full analysis set; OSDI, Ocular Surface Disease Index; SS, Sjögren's syndrome.

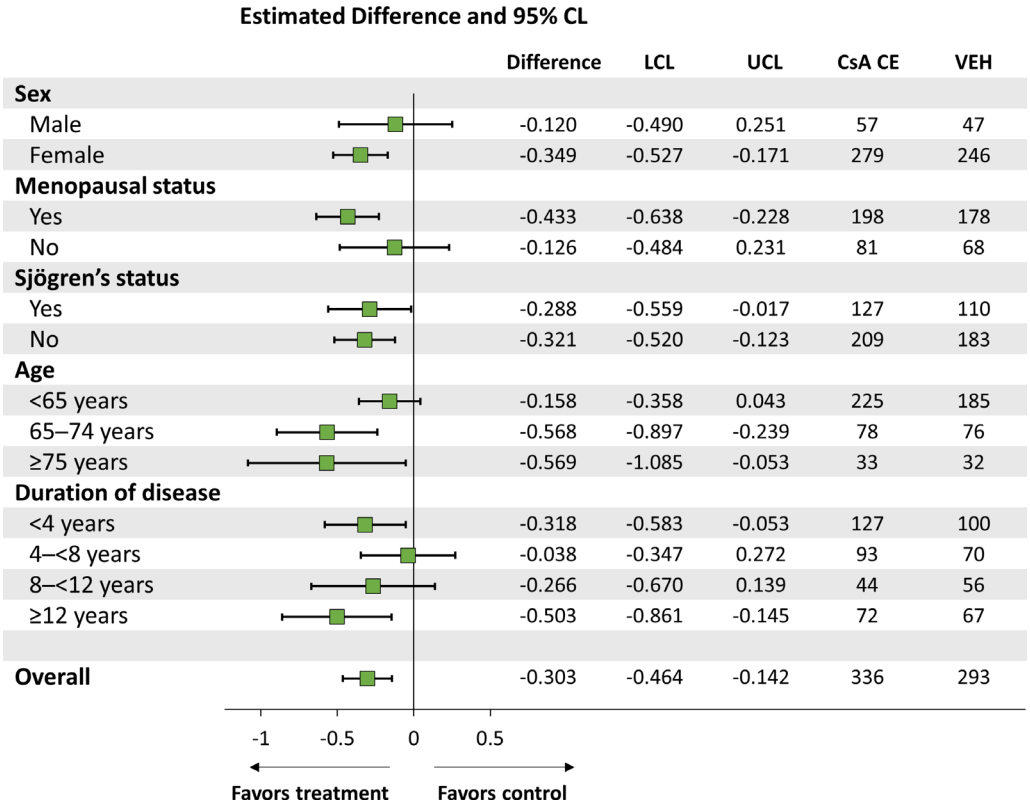

Figure 3 Change from baseline in CFS score at month 6 by patient subgroup in the pooled analysis (n=629). Green boxes represent the estimate of the difference between groups (least-squares means). Horizontal lines are 95% confidence limits. CFS, corneal fluorescein staining; CL, confidence limit; CsA CE, 0.1% (1 mg/mL) ciclosporin A in a cationic emulsion; LCL, lower confidence limit; UCL, upper confidence limit; VEH, vehicle.

population (figure 2A–D). In the FAS (all DED patients) population (figure 2A), the OR and the 95% CI were 1.66 (1.11 to 2.50), and in the subgroup of patients with severe DED, the corresponding values were 1.80 (1.04 to 3.19) (figure 2B). The OR and 95% CI in the SS/severe DED population also favoured CsA CE treatment and indicated a three-times-greater probability of response over vehicle in this patient population (OR 3.37; 1.20 to 11.19) (figure 2D).

Corneal fluorescein staining

Improvements in CFS score at month 6 favoured CsA CE over vehicle in the overall population (treatment difference –0.303; 95% confidence limit (CL) –0.464 to –0.142) (figure 3). A significant treatment effect in favour of CsA CE was observed in most patient subgroups in the pooled analysis. Clinical benefit with CsA CE was most notable in elderly patients (65–74 years of age: treatment difference –0.568, 95% CL –0.897 to –0.239; ≥75 years of age: –0.569, –1.085 to –0.053), female patients (–0.349, –0.527 to –0.171) and menopausal patients (–0.433, –0.638 to –0.228). Treatment with CsA CE also produced improvements in CFS score regardless of SS status (SS –0.288, –0.559 to –0.017; no SS –0.321, –0.520 to –0.123).

Ocular surface inflammation and relationship to DED severity

For the 168 patients with HLA-DR data at baseline and month 6, baseline HLA-DR expression values were directly proportional to CFS score, indicating that patients with more severe DED had increased ocular inflammation. Figure 4 shows change in HLA-DR expression in median arbitrary units of fluorescence according to baseline CFS score subgroups (CFS=2, 3 or 4). Overall, CsA CE was significantly more effective versus vehicle in reducing ocular inflammation from baseline to month 6 (P=0.002). Notably, while reductions in HLA-DR expression were observed with CsA CE for each CFS subgroup, and to a lesser extent for vehicle with the CFS=2 and CFS=4 subgroups, an increase in HLA-DR expression was seen among patients receiving vehicle in the CFS=3 subgroup.

Safety findings

Drug-related treatment-emergent adverse events (TEAEs) were reported in 35.9% of CsA CE patients and 20.3% of vehicle patients in the pooled analysis (online supplementary table 1). Drug-related TEAEs were mostly ocular in nature, with no reported incidence of serious systemic events. The most frequently reported ocular TEAEs deemed possibly related to CsA CE treatment were instillation site pain (12.1%), eye irritation (10.1%) and instillation site irritation (5.1%). Two patients experienced serious drug-related ocular TEAEs: one patient in the CsA CE group had severe corneal epithelial erosion that resolved without sequelae, and one patient in the vehicle group had decreased BCDVA; both discontinued therapy. Overall, study discontinuation due to drug-related ocular TEAEs was reported in 9.3% of CsA CE patients and 5.9% of vehicle patients.

There were no clinically significant changes in blood pressure, pulse rate or respiratory rate in either treatment group during the 6-month course of the studies; BCDVA and IOP also remained stable. At baseline, five patients presented with a serum CsA value greater than the upper limit of quantification (5.0 mg/mL; ie, CsA levels that could be reliably quantified); these patients were already receiving systemic CsA at a stable dose (as allowed by the study protocols). At the month 6 visit, 35 patients had a detectable serum CsA level that was below the upper limit

of quantification (ie, CsA levels that could be detected but not reliably quantified), and 11 patients had a quantifiable serum value; the latter values were considered negligible (highest value 0.206 ng/mL).

DISCUSSION

This analysis of pooled data from the SICCANOVE and SANSIKA studies provides a representative estimation of the efficacy and safety of CsA CE in the treatment of moderate-to-severe DED. CsA CE was statistically superior to vehicle in improving both signs and symptoms of DED in the overall patient population (especially in those with severe keratitis) and in patients with SS/severe DED, and there was a trend towards greater benefits in the overall Sjögren's population; CsA CE also demonstrated a safety profile consistent with ophthalmic CsA use.

Results in this pooled analysis were generally consistent with those in the SANSIKA study, which used the composite CFS–OSDI response rate as its primary signs and symptoms endpoint. The SANSIKA study found a CFS–OSDI response rate of 28.6% in the CsA CE group and 23.1% in the vehicle group (P=0.326).[15] Although statistical significance was not achieved for CsA CE compared with vehicle in SANSIKA, it should be noted that statistical significance was achieved when the threshold for improvement of CFS was increased from 2 grades to 3 grades in a post hoc analysis.[15] Lack of statistical significance for the primary endpoint in the SANSIKA study may have been due to the marked improvement seen with the vehicle, which is an unpreserved cationic oil-in-water nanoemulsion that can have a beneficial effect on DED symptoms through improved lubrication and hydration.[14 18] Discordance between signs and symptoms of DED has been a challenge in the conduct of DED studies.[19–21] In this respect, the composite endpoint provides a useful joint assessment of signs and symptoms in such a multifaceted disease; this approach has also been proposed in other chronic inflammatory diseases (eg, fibromyalgia, rheumatoid arthritis).[22]

The results for CFS change from baseline in this pooled analysis were consistent with those obtained in both studies; a mean treatment difference between CsA CE and vehicle of –0.303 (95% CL –0.464 to –0.142) was observed for the overall patient population in the pooled analysis, as compared with a mean treatment difference of –0.22 (95% CI –0.39 to –0.06) and –0.35 (95% CI –0.671 to –0.021) in SICCANOVE and SANSIKA, respectively; all results were statistically significant.[15 16] According to the logarithmic nature of the modified Oxford scale, these findings correspond to 30%–50% more punctate epithelial damage of the cornea in the vehicle group versus the treatment groups. The improvement observed with CsA CE, particularly in the more severe populations, supports the primary goal for treatment of moderate-to-severe DED—namely, to maintain and protect the ocular surface.[23]

CsA CE also improved signs and symptoms (as assessed by CFS–OSDI response) in patients with SS, although the superiority over vehicle was statistically significant only in the subset of patients with both SS and severe DED. These findings are of importance, given that DED in patients who have SS, an autoimmune form of aqueous-deficient dry eye, is typically more severe and difficult to treat than in patients without SS.[24 25] A clear association between ocular surface inflammation (HLA-DR expression as assessed by conjunctival impression cytology) and DED severity was also observed,[26] and CsA CE significantly reduced HLA-DR expression compared with vehicle at month 6 (overall treatment difference: P=0.002). This effect of CsA CE on HLA-DR likely derives from CsA CE's anti-inflammatory properties,[26–28] and results from this pooled analysis support the use of HLA-DR expression level as a biomarker to monitor treatment response in patients with DED.

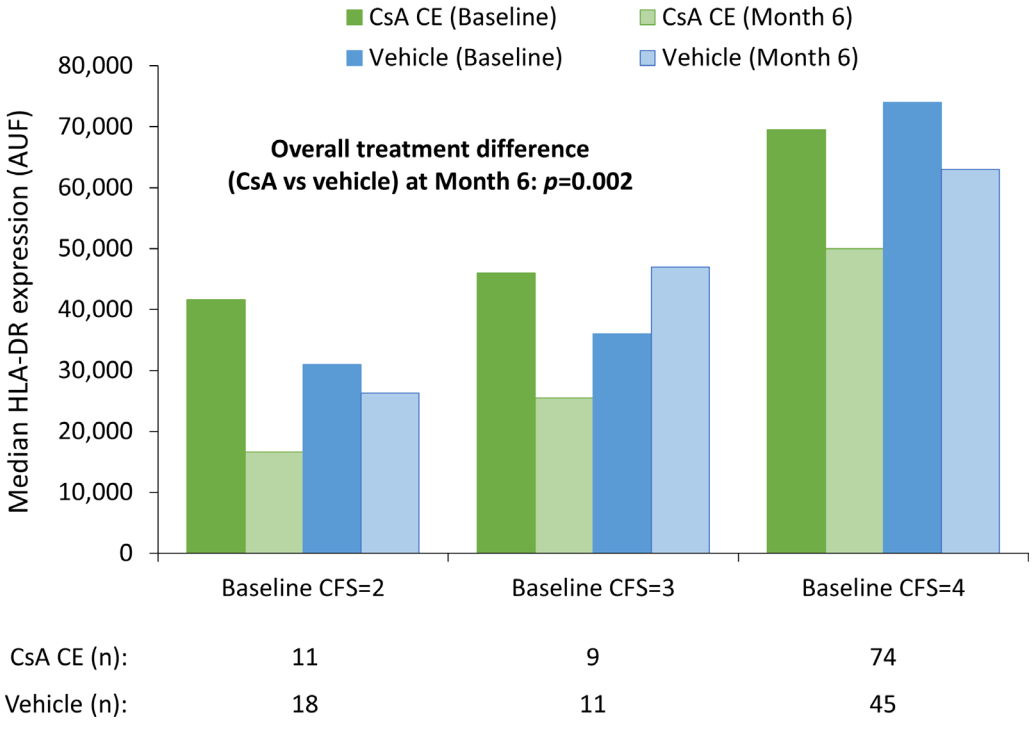

Figure 4 Pooled analysis of the relationship between CFS score and HLA-DR expression (as assessed by impression cytology). AUF, arbitrary units of fluorescence; CFS, corneal fluorescein staining; CsA CE, 0.1% (1 mg/mL) ciclosporin A in a cationic emulsion; HLA-DR, human leucocyte antigen-DR.

Limitations of this pooled analysis include differences in entry criteria for the two studies (moderate-to-severe DED for SICCANOVE vs severe DED for SANSIKA), which may limit comparability of the results. However, it should be noted that when applying the ODISSEY algorithm for establishing the severity of DED,[29] both populations are categorised as predominantly having severe disease (86.5% in SICCANOVE and 98% in SANSIKA at baseline).[30] Interestingly, from a geographical perspective, the two studies were conducted in Europe in the same countries (Spain, France, UK, Italy, Czech Republic and Germany) and many of the same clinical centres, with the exception that SANSIKA also recruited patients in Austria and Belgium. Moreover, the recruitment was conducted over multiple months for both studies (18 months for SICCANOVE and 10 months for SANSIKA) in order to avoid biases from seasonal and weather-related conditions.[31]

In conclusion, the combined efficacy and safety data from this pooled analysis suggest that CsA CE—a novel formulation of unpreserved single-dose cationic emulsion of ciclosporin 0.1%—has a favourable safety and tolerability profile and is efficacious in improving both signs and symptoms of DED in patients with moderate-to-severe DED (especially those with severe keratitis), including patients with SS with severe DED.

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Correction notice This article has been corrected since it was published Online First. The Correspondence to address has been changed to "Giustiniani 2, 35128 Padova, Italy".

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Contributors MA, J-SG, DI and CB contributed to the initial study design. MA, DI and CB wrote the protocol and its amendments. MA, DI and CB reviewed the data quality prior to database lock. AL, EMM, ML, MS-d-l-M, FCF and CB contributed to the acquisition of data. AL, MA, J-SG, DI and CB contributed to the analysis and interpretation of data. MA and DI wrote the first draft of the manuscript with medical-writing assistance (funded by Santen). AL, EMM, ML, MA, J-SG, DI, MS-d-l-M, FCF and CB participated in the drafting and critical revision of the manuscript. All authors had full access to the data in the study and were required to approve the manuscript for submission and publication. AL made the final decision to submit the manuscript for publication. AL is the guarantor of this work and, as such, takes responsibility for the fidelity of the trial to the protocol and the completeness and accuracy of the data.

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Competing interests AL is a consultant for, or has received a research grant from, Allergan, Alcon, MediVis, Santen, SIFI and Théa and was an investigator in the SICCANOVE and SANSIKA studies. EMM is a consultant for, or has received speaker honoraria from, Alcon Pharma GmbH, Dompé, Pharm-Allergan GmbH, Santen GmbH, Shire, Théa Pharma GmbH, TRB Chemedica AG, Ursapharm and VISUfarma and was an investigator in the SICCANOVE study. ML is a consultant for, or has received a research grant from, Alcon, Allergan, Bausch & Lomb, Dompé, Santen and Théa and was an investigator in the SICCANOVE and SANSIKA studies. MA is an employee of Santen SAS. J-SG is an employee of Santen SAS. DI is an employee of Santen SAS. MS-d-l-M is a consultant for Santen and was an investigator in the SICCANOVE and SANSIKA studies. FCF is a consultant for, or has received a research grant from, Allergan, Théa and Santen and was an investigator in the SICCANOVE and SANSIKA studies. CB is a consultant for, or has received a research grant from, Alcon, Allergan, Santen and Théa and was a clinical investigator in the SICCANOVE and SANSIKA studies.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval Both studies described in our article were conducted in accordance with the principles of Good Clinical Practice and with the ethical principles set out in the Declaration of Helsinki. All enrolled patients provided written informed consent. The studies were registered under the following numbers in the EudraCT database: 2011-000160-97 and 2007-000029-23.

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