

# One-year efficacy and safety of 0.1% cyclosporine A cationic emulsion in the treatment of severe dry eye disease

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## ABSTRACT

**Purpose:** The SANSIKA study evaluated the efficacy/safety of 0.1% (1 mg/mL) cyclosporine A cationic emulsion (CsA CE) for treating dry eye disease (DED) with severe keratitis. The double-masked phase demonstrated that CsA CE was effective in reducing corneal damage and ocular surface inflammation, and was well-tolerated over 6 months. Here we report efficacy and safety findings of SANSIKA's open-label extension (OLE).

**Methods:** In this multicenter, double-masked, phase III study, patients with severe DED (corneal fluorescein staining [CFS] grade 4, modified Oxford scale) were randomized to once-daily CsA CE (Ikervis<sup>®</sup>) or its vehicle for 6 months, followed by 6-month open-label, once-daily CsA CE (CsA CE/CsA CE and vehicle/CsA CE groups).

**Results:** A total of 177 patients completed the OLE. Efficacy results reiterated the double-masked phase: CsA CE reduced CFS score and human leukocyte antigen-antigen D related expression, improved corneal clearing, and produced continuous improvements in global symptom scores (ocular surface disease index [OSDI], visual analogue scale). The CFS-OSDI response rates ( $\geq 2$  CFS points,  $\geq 30\%$  OSDI improvement vs baseline) at 12 vs 6 months were 39.1% vs 28.6%, respectively, for CsA CE/CsA CE and 38.0% vs 23.1% for vehicle/CsA CE. Cyclosporine A CE's safety profile was similar to the initial 6 months. The most common treatment-related treatment-emergent adverse event was instillation site pain (7.8%, CsA CE/CsA CE group; 19.0%, vehicle/CsA CE group). No unexpected safety signals were observed; systemic CsA levels were undetectable/negligible in all patients except 2 previously treated with systemic CsA.

**Conclusions:** In this 12-month study, once-daily CsA CE was well-tolerated and showed reductions in ocular surface inflammation and improvements in signs/symptoms in DED patients with severe keratitis.

**Keywords:** Cationic emulsion, Cyclosporine, Inflammation, Keratoconjunctivitis sicca, Open-label extension, Severe keratitis

## Introduction

Dry eye disease (DED) is a multifactorial disease of the tear film and ocular surface that can produce debilitating symptoms such as ocular pain, burning, dryness, foreign body

sensation, and visual disturbances (1, 2). It is one of the most common ophthalmic conditions, with a prevalence ranging from 5% to 35% (2). In DED pathophysiology, tear hyperosmolarity triggers a cascade of inflammatory events, which in turn exacerbate the underlying tear film instability and perpetuate the disease process (3). Elevated levels of human leukocyte antigen-antigen D related (HLA-DR), an inflammatory biomarker, provide further evidence for the involvement of an inflammatory process in aggravating the signs and symptoms and severity of DED (4, 5).

While topical corticosteroids have been shown to be effective in improving the signs and symptoms of DED, side effects such as intraocular hypertension and cataracts render them unsuitable for long-term treatment (6, 7). Artificial tear formulations have also proven useful in some DED patients, but

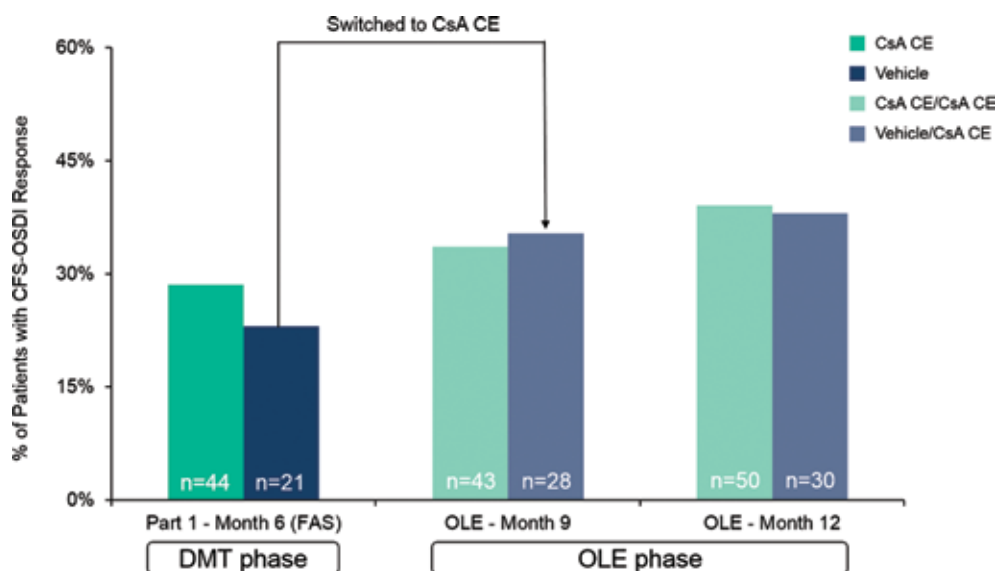
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**Fig. 1** - Corneal fluorescein staining ocular surface disease index (CFS-OSDI) responder rates over time. Patients randomized to 0.1% (1 mg/mL) cyclosporine A cationic emulsion (CsA CE) or vehicle during part 1 were switched to open-label CsA CE during part 2 (CsA CE/CsA CE and vehicle/CsA CE groups, respectively). Data represent responder rates of the full analysis set population. DMT = double-masked treatment; FAS = full analysis set; OLE = open-label extension.

only provide short-term symptom relief (8). The use of immunosuppressive agents to control the inflammatory responses has also been demonstrated to be effective for treatment of signs and symptoms associated with DED (8). Cyclosporine A (CsA) has been shown to be well-tolerated when administered to patients for long-term management of DED (9).

For lipophilic drugs such as cyclosporine, encapsulation in a cationic emulsion may promote precorneal residence time of the drug and its productive bioavailability at the ocular surface, as well as increased corneal penetration (10, 11). Santen SAS developed a cationic emulsion containing unpreserved 0.1% (1 mg/mL) cyclosporine A (CsA CE; Ikervis®) as a topical formulation for treating severe forms of immune-mediated ocular surface diseases such as DED (10, 12). The phase III, multicenter, randomized, vehicle-controlled, parallel-group SANSIKA study assessed the safety and efficacy of once-daily CsA CE for patients with severe DED (13) in a double-masked fashion for the first 6 months, followed by a 6-month open-label extension (OLE). The results from the double-masked segment of the SANSIKA trial showed the efficacy of once-daily CsA CE in reducing corneal damage and ocular surface inflammation in adults with severe keratitis in DED. This pivotal study supported the approval of CsA CE by the European Medicines Agency in 2015 for treatment of severe keratitis in DED that is refractory to tear substitutes. Here, we report the findings of the 6-month OLE of SANSIKA, providing descriptive analysis on the efficacy and safety of CsA CE over a 12-month period.

## Methods

### Participants

Eligibility criteria for the SANSIKA study have been described previously (13). Briefly, the study enrolled adult patients ( $\geq 18$  years) with severe DED, as determined by corneal fluorescein staining (CFS) grade 4 (on a modified Oxford scale, from 0-5) (14); a Schirmer test score without anesthesia  $\geq 2$  mm/5 min and  $< 10$  mm/5 min (15); and an ocular surface disease index (OSDI) score  $\geq 23$  (16).

### Study design

As described previously (13), the phase III SANSIKA study, which was conducted in 50 centers across 9 European countries (France, Germany, Italy, Spain, Belgium, United Kingdom, Sweden, Austria, and the Czech Republic), comprised 2 parts: a 6-month, multicenter, randomized, double-masked, vehicle-controlled, parallel-group period (part 1), followed by a 6-month, open-label follow-up period (part 2) (see supplementary Fig. 1, available online as supplementary material at [www.eur-j-ophthalmol.com](http://www.eur-j-ophthalmol.com)). During the OLE, all patients were asked to administer 1 drop of unpreserved single-dose CsA CE 0.1% (1 mg/mL) once daily at bedtime. Throughout the 12-month study, patients were allowed to use unpreserved artificial tears (AT) provided by the sponsor as frequently as needed for DED symptom relief (saline solution, Larmabak®; Théa). For the subset of patients participating in part 2, efficacy and safety data were assessed at the month 6, 9, and 12 visits postrandomization.

All enrolled patients provided written informed consent, and the study was conducted in accordance with good clinical practice and ethical principles in the Declaration of Helsinki. This study was registered in the EudraCT database (2011-000160-97), with the protocol code number NVG10E117 (17). Full details regarding efficacy and safety assessments and statistical analyses are presented in the supplementary appendix, available online as supplementary material at [www.eur-j-ophthalmol.com](http://www.eur-j-ophthalmol.com).

## Results

### Patient demographics and disposition

Of the 245 patients analyzed in the full analysis set in the SANSIKA study (154 in the CsA CE group and 91 in the vehicle group [13]), 207 (84%) patients received CsA CE in the OLE (see supplementary Fig. 1, available online at [www.eur-j-ophthalmol.com](http://www.eur-j-ophthalmol.com)). This included 128 (83.1%) patients continuing on CsA CE in the OLE (CsA CE/CsA CE group)

**TABLE I** - Responder rates for key efficacy variables at months 6 and 12<sup>a</sup>

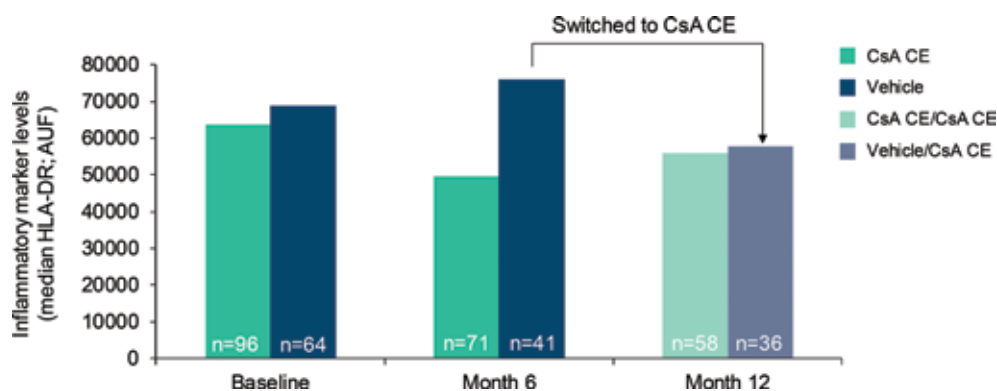
|                                                                                  | Month 6 (part 1) <sup>b</sup> |                        | Month 12 (part 2)          |                            |
|----------------------------------------------------------------------------------|-------------------------------|------------------------|----------------------------|----------------------------|
|                                                                                  | CsA CE<br>(n = 154)           | Vehicle<br>(n = 91)    | CsA CE/CsA CE<br>(n = 128) | Vehicle/CsA CE<br>(n = 79) |
| CFS-OSDI response (improvement $\geq 2$ grades for CFS and $\geq 30\%$ for OSDI) | 44 (28.6) [21.6, 36.4]        | 21 (23.1) [14.9, 33.1] | 50 (39.1) [30.6, 48.1]     | 30 (38.0) [27.3, 49.6]     |
| CFS response (improvement $\geq 2$ grades)                                       | 80 (51.9) [43.8, 60.1]        | 41 (45.1) [34.6, 55.8] | 84 (65.6) [56.7, 73.8]     | 43 (54.4) [42.8, 65.7]     |
| CFS response (improvement $\geq 3$ grades, post hoc)                             | 48 (31.2) [24.5, 39.8]        | 12 (13.2) [7.0, 21.9]  | 54 (42.2) [33.5, 51.2]     | 25 (31.7) [21.6, 43.1]     |
| OSDI response (improvement $\geq 30\%$ )                                         | 61 (39.6) [31.8, 47.8]        | 36 (39.6) [29.5, 50.4] | 67 (52.3) [43.3, 61.2]     | 44 (55.7) [44.1, 66.9]     |
| Global VAS response (improvement $\geq 30\%$ )                                   | 48 (31.2) [24.0, 39.1]        | 34 (37.4) [27.4, 48.1] | 69 (53.9) [44.9, 62.8]     | 41 (51.9) [40.4, 63.3]     |
| CFS-VAS response (improvement $\geq 2$ grades for CFS and $\geq 30\%$ for VAS)   | 35 (22.7) [16.4, 30.2]        | 19 (20.9) [13.1, 30.7] | 54 (42.2) [33.5, 51.2]     | 32 (40.5) [29.6, 52.1]     |

Values are n (%) [95% confidence interval].

<sup>a</sup> Responder criteria based on improvements vs SANSIKA part 1 baseline. Data shown are imputed data.

<sup>b</sup> Month 6 responder rates have been published previously (13).

CFS = corneal fluorescein staining; CsA CE = 0.1% (1 mg/mL) cyclosporine A cationic emulsion; OSDI = ocular surface disease index; VAS = visual analogue scale.



**Fig. 2** - Median human leukocyte antigen-antigen D related (HLA-DR) scores over time. Patients randomized to 0.1% (1 mg/mL) cyclosporine A cationic emulsion (CsA CE) or vehicle during part 1 were switched to open-label CsA CE during part 2 (CsA CE/CsA CE and vehicle/CsA CE groups, respectively). Baseline data are based on the patient population who participated in part 2 of the study. AUF = arbitrary units of fluorescence.

and 79 (86.8%) patients switched from vehicle to CsA CE (vehicle/CsA CE group). Demographics and disease characteristics were similar between groups (see supplementary Tab. I, available online at [www.eur-j-ophthalmol.com](http://www.eur-j-ophthalmol.com)). A total of 177 patients enrolled in SANSIKA completed the month 12 visit.

### Efficacy results

#### CFS-OSDI responder rates

The proportion of patients categorized as CFS-OSDI responders at the end of month 12 (demonstrated improvement of  $\geq 2$  grades in CFS and improvement of  $\geq 30\%$  in OSDI from SANSIKA part 1 baseline) increased markedly in both the CsA CE/CsA CE and vehicle/CsA CE group (Fig. 1). Responder rates rose to 33.6% (95% confidence interval [CI] 25.5%-42.5%) at month 9 and 39.1% (95% CI 30.6%-48.1%) at month 12 in the CsA CE/CsA CE group and to 35.4% (95% CI 25.0%-47.0%) at month 9 and 38.0% (95% CI 27.3%-49.6%) at month 12 in the vehicle/CsA CE group (Tab. I).

The cumulative results of parts 1 and 2 of the SANSIKA study demonstrate a continuous increase in the CFS-OSDI responder rate over the 12-month period in both groups. The sharpest increase in responder rates occurred between months 6 and 9, among patients who switched from vehicle to CsA CE.

#### Corneal fluorescein staining

Statistically significant reduction in mean CFS was observed with CsA CE vs vehicle at month 3 and 6 of part 1 of the SANSIKA study (13). Continuous improvements in both the CsA CE/CsA CE and vehicle/CsA CE groups were observed between months 6 and 12 during the OLE period (see supplementary Fig. 2A, available online at [www.eur-j-ophthalmol.com](http://www.eur-j-ophthalmol.com)). Mean ( $\pm$ SD) CFS scores were  $2.14 \pm 1.25$  and  $2.53 \pm 1.11$  at month 6 and  $1.73 \pm 1.14$  and  $2.00 \pm 1.30$  at month 12 for the CsA CE/CsA CE and vehicle/CsA CE group, respectively.

The percentage of patients who showed an improvement of  $\geq 2$  grades from baseline was higher in the CsA CE/CsA CE group (65.6%) vs the vehicle/CsA CE group (54.4%)

at month 12 (Tab. I). A higher proportion of responders was also observed in the CsA CE/CsA CE group compared with the vehicle/CsA CE group for patients who had an improvement of  $\geq 3$  grades from baseline (i.e., absent or minimal corneal damage [CFS score = 0, 0.5, or 1]; 42.2% vs 31.7%, respectively, at month 12) (post hoc analysis; Tab. I). The proportion of patients with complete corneal clearing (CFS score = 0) approximately doubled at month 12 vs month 6 in the CsA CE/CsA CE group (12.5% vs 6.5%). A greater change was seen in the vehicle/CsA CE group, where corneal clearing was observed in 4.4% of patients at month 6 and 11.4% at month 12 (see supplementary Fig. 2B, available online at [www.eur-j-ophthalmol.com](http://www.eur-j-ophthalmol.com)).

### Ocular surface inflammation

Significant reductions in median expression of HLA-DR by conjunctival epithelial cells (as assessed by impression cytology) were observed with CsA CE vs vehicle in part 1 of the SANSIKA study (13). Patients continuing on CsA CE in part 2 largely maintained the HLA-DR reductions from baseline achieved in part 1, and patients switching to CsA CE from vehicle demonstrated marked reductions in HLA-DR at month 12 (median HLA-DR levels of 63,848, 49,751, and 56,045 arbitrary units of fluorescence [AUF] at baseline, month 6, and month 12, respectively, for the CsA CE/CsA CE group, with corresponding values of 68,956, 76,062, and 57,728 AUF for the vehicle/CsA CE group) (Fig. 2).

### Symptomatology

At month 12, a majority of patients showed improvements in symptoms. Mean scores for OSDI (see supplementary Fig. 3 and Tab. II, available online as supplementary material at [www.eur-j-ophthalmol.com](http://www.eur-j-ophthalmol.com)) and global visual analogue scale (VAS) (Tab. II) decreased steadily between baseline and month 12 for both the CsA CE/CsA CE and vehicle/CsA CE groups (mean [ $\pm$ SD] changes from baseline in OSDI scores of  $-14.80 \pm 21.06$  and  $-20.21 \pm 21.36$  at month 6 and month 12, respectively, for the CsA CE/CsA CE group, with corresponding values of  $-13.29 \pm 19.13$  and  $-21.49 \pm 19.87$  for the vehicle/CsA CE group; mean [ $\pm$ SD] changes from baseline in global VAS scores of  $-13.76 \pm 22.16$  and  $-21.41 \pm 24.01$  at month 6 and month 12, respectively, for the CsA CE/CsA CE group, with corresponding values of  $-10.51 \pm 21.97$  and  $-18.98 \pm 23.38$  for the vehicle/CsA CE group). In general, the greatest symptomatic improvements were observed during the first 6 months of treatment.

### Other efficacy analyses

Responder rates (OSDI, global VAS, and CFS-VAS) increased between month 6 and month 12, with no noticeable differences between the groups (Tab. I). Mean scores for lissamine green staining decreased (i.e., improved) between baseline and month 6 and then remained stable until month 12 in both treatment groups (Tab. II). Other variables (Schirmer test, tear film break-up time, National Eye Institute Visual Function Questionnaire-25, and European Quality of Life-5 Dimensions Questionnaire) remained relatively stable in both treatment groups (Tab. II). Analyses for use of AT and tear film osmolarity were hampered by low sample sizes for both treatment groups.

**TABLE II** - Efficacy assessments: change from baseline at months 6 and 12

|                            | CsA CE/CsA CE                                             | Vehicle/CsA CE                                           |
|----------------------------|-----------------------------------------------------------|----------------------------------------------------------|
| OSDI score                 |                                                           |                                                          |
| Change at month 6          | (n = 128)<br>$-14.80 \pm 21.06$<br>$-14.58 (-79.2, 45.6)$ | (n = 79)<br>$-13.29 \pm 19.13$<br>$-13.64 (-60.4, 32.5)$ |
| Change at month 12         | (n = 114)<br>$-20.21 \pm 21.36$<br>$-20.00 (-69.4, 43.3)$ | (n = 65)<br>$-21.49 \pm 19.87$<br>$-20.45 (-60.4, 21.3)$ |
| Global VAS assessment      |                                                           |                                                          |
| Change at month 6          | (n = 118)<br>$-13.76 \pm 22.16$<br>$-11.55 (-59.8, 66.6)$ | (n = 72)<br>$-10.51 \pm 21.97$<br>$-9.93 (-59.5, 38.5)$  |
| Change at month 12         | (n = 105)<br>$-21.41 \pm 24.01$<br>$-21.63 (-85.5, 22.8)$ | (n = 59)<br>$-18.98 \pm 23.38$<br>$-20.75 (-63.1, 35.6)$ |
| Schirmer test, mm/5 min    |                                                           |                                                          |
| Change at month 6          | (n = 127)<br>$2.39 \pm 5.99$<br>$1.00 (-7.0, 32.0)$       | (n = 76)<br>$1.40 \pm 3.84$<br>$1.00 (-5.0, 18.0)$       |
| Change at month 12         | (n = 122)<br>$2.30 \pm 5.05$<br>$1.00 (-6.0, 29.0)$       | (n = 69)<br>$1.52 \pm 4.20$<br>$1.00 (-8.0, 20.0)$       |
| Lissamine green staining   |                                                           |                                                          |
| Change at month 6          | (n = 111)<br>$-1.78 \pm 2.10$<br>$-2.00 (-6.0, 4.0)$      | (n = 68)<br>$-1.53 \pm 2.15$<br>$-1.00 (-9.0, 5.0)$      |
| Change at month 12         | (n = 99)<br>$-1.81 \pm 2.01$<br>$-1.00 (-8.0, 3.0)$       | (n = 54)<br>$-1.69 \pm 2.84$<br>$-2.00 (-8.0, 5.0)$      |
| TBUT                       |                                                           |                                                          |
| Change at month 6          | (n = 127)<br>$0.74 \pm 2.10$<br>$0.50 (-5.0, 8.7)$        | (n = 79)<br>$0.33 \pm 1.78$<br>$0.00 (-4.5, 7.8)$        |
| Change at month 12         | (n = 125)<br>$0.90 \pm 2.14$<br>$0.50 (-4.0, 7.3)$        | (n = 72)<br>$0.33 \pm 1.85$<br>$0.00 (-4.5, 5.5)$        |
| NEI-VFQ-25 composite score |                                                           |                                                          |
| Change at month 6          | (n = 74)<br>$4.80 \pm 8.62$<br>$4.60 (-15.7, 32.3)$       | (n = 43)<br>$4.86 \pm 10.09$<br>$4.36 (-21.2, 24.7)$     |
| Change at month 12         | (n = 70)<br>$4.88 \pm 9.15$<br>$4.79 (-14.2, 23.8)$       | (n = 34)<br>$6.87 \pm 10.45$<br>$7.25 (-22.2, 31.4)$     |
| EQ-5D summary index        |                                                           |                                                          |
| Change at month 6          | (n = 119)<br>$0.02 \pm 0.25$<br>$0.00 (-0.9, 0.8)$        | (n = 72)<br>$0.02 \pm 0.22$<br>$0.00 (-0.8, 0.7)$        |
| Change at month 12         | (n = 118)<br>$0.05 \pm 0.25$<br>$0.0 (-0.6, 0.7)$         | (n = 65)<br>$0.05 \pm 0.25$<br>$0.00 (-0.6, 0.8)$        |

Values are mean  $\pm$  SD and median (min, max).

CsA CE = 0.1% (1 mg/mL) cyclosporine A cationic emulsion; EQ-5D = European Quality of Life-5 Dimensions Questionnaire; NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire-25; OSDI = Ocular Surface Disease Index; TBUT = tear film break-up time; VAS = visual analogue scale.

**TABLE III** - Adverse events recorded for all patients at month 6 (SANSIKA part 1) and from month 6 to month 12 (part 2) (SAF)

|                                                         | CsA CE, 6 months<br>(n = 154) | Vehicle, 6 months<br>(n = 90) | CsA CE/CsA CE,<br>6-12 months (n = 128) | Vehicle/CsA CE,<br>6-12 months (n = 79) |
|---------------------------------------------------------|-------------------------------|-------------------------------|-----------------------------------------|-----------------------------------------|
| Any TEAE <sup>a</sup>                                   | 88 (57.1)                     | 42 (46.7)                     | 54 (42.2)                               | 28 (35.4)                               |
| Any treatment-related TEAE                              | 57 (37.0)                     | 19 (21.1)                     | 19 (14.8)                               | 18 (22.8)                               |
| Any ocular TEAE                                         | 66 (42.9)                     | 27 (30.0)                     | 34 (26.6)                               | 23 (29.1)                               |
| Any treatment-related ocular TEAE                       | 57 (37.0)                     | 18 (20.0)                     | 19 (14.8)                               | 18 (22.8)                               |
| Any TEAE leading to discontinuation <sup>b</sup>        | 21 (13.6)                     | 9 (10.0)                      | 10 (7.8)                                | 9 (11.4)                                |
| Any ocular TEAE leading to discontinuation <sup>b</sup> | 18 (11.7)                     | 6 (6.7)                       | 9 (7.0)                                 | 7 (8.9)                                 |
| Treatment-related TEAE leading to discontinuation       | 16 (10.4)                     | 5 (5.6)                       | 8 (6.3)                                 | 7 (8.9)                                 |
| Any severe ocular TEAE <sup>c</sup>                     | 9 (5.8)                       | 5 (5.6)                       | 1 (0.8)                                 | 1 (1.3)                                 |
| Any SAE <sup>d</sup>                                    | 6 (3.9)                       | 6 (6.7)                       | 8 (6.3)                                 | 2 (2.5)                                 |
| Any treatment-related SAE                               | 0                             | 1 (1.1)                       | 0                                       | 0                                       |
| Any ocular SAE                                          | 0                             | 1 (1.1)                       | 0                                       | 0                                       |
| Deaths                                                  | 0                             | 0                             | 0                                       | 0                                       |

Values are n (%).

<sup>a</sup> An adverse event was considered to be a TEAE if the date of onset of the event was on or after the date of the first study drug dose.

<sup>b</sup> Includes TEAEs that started during part 2 and led to permanent discontinuation during part 2, as well as 4 TEAEs that started during part 1 and led to permanent discontinuation during part 2 (3 cases of instillation site pain and 1 of staphylococcal infection, all in the CsA CE/CsA CE group).

<sup>c</sup> Severe events were defined as being very stressful and interfering with normal daily life.

<sup>d</sup> An SAE was defined as any untoward medical occurrence or effect that resulted in death; was life-threatening (i.e., the patient was at an immediate risk of death as a result of the adverse event); required inpatient hospitalization (for >24 hours) or prolongation of existing hospitalization (except when hospitalization was planned before the patient's enrollment in the study); resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; or was an important medical event.

CsA CE = 0.1% (1 mg/mL) cyclosporine A cationic emulsion; SAE = serious adverse event; SAF = safety analysis set; TEAE = treatment-emergent adverse event.

### Compliance/adherence

Most patients complied with the prescribed treatment regimen of once-daily CsA CE throughout the 12-month course of the SANSIKA study, with percentages ranging from 76.0% to 83.1%, depending on the study period. Adherence to the eyedrop instillation instructions was also high throughout the study. During part 1, instillation was performed on 94.5% and 96.5% of days by patients in the CsA CE and vehicle groups, respectively, during the period from baseline to month 1; the corresponding values were 95.1% and 98.8% for months 1 to 3 and 97.8% and 97.9% for months 3 to 6. During part 2, instillation was performed on 94.7% and 93.1% of days by patients in the CsA CE/CsA CE and vehicle/CsA CE groups, respectively, from months 6 to 9; the corresponding values were 95.1% and 97.5% for months 9 to 12.

### Safety results

Safety analyses over 12 months were conducted in 154 patients who received CsA CE treatment during part 1 of the study (safety analysis set; mean duration of CsA CE therapy, 302.31 days), as well as the CsA CE/CsA CE (n = 128) and vehicle/CsA CE (n = 79) groups from part 2. Safety analyses from

part 1 of this study have been published previously (13). A summary of adverse events from part 1 and part 2 is presented in Table III. As in part 1, most treatment-emergent adverse events (TEAEs) reported in part 2 were ocular in nature and there were no ocular serious adverse events reported in either group.

Treatment-related TEAEs during part 2 were reported in 19 patients (14.8%) in the CsA CE/CsA CE group and 18 patients (22.8%) in the vehicle/CsA CE group (Tab. III). In the vehicle/CsA CE group, all treatment-related TEAEs were ocular. In the CsA CE/CsA CE group, all treatment-related TEAEs were ocular, with the following exceptions: stomatitis (1 patient, 0.8%), fatigue (1 patient, 0.8%), headache (1 patient, 0.8%), and increased upper airway secretion (1 patient, 0.8%). Considering nonocular events only, there were no trends for an increased incidence of treatment-related TEAEs with either treatment.

Treatment-related ocular TEAEs were reported in 19 patients (14.8%) in the CsA CE/CsA CE group and 18 patients (22.8%) in the vehicle/CsA CE group (Tab. III).

The most common treatment-related ocular TEAE in part 2 was instillation site pain, which was reported in 10 patients (7.8%) in the CsA CE/CsA CE group and 15 patients (19.0%) in the vehicle/CsA CE group (Tab. IV). Apart from instillation



**TABLE IV** - Incidence of treatment-related TEAEs occurring in >1% of patients receiving CsA CE during part 2 of the SANSIKA study (SAF)<sup>a</sup>

|                            | CsA CE/CsA CE<br>(n = 128) | Vehicle/CsA CE<br>(n = 79) |
|----------------------------|----------------------------|----------------------------|
| Any treatment-related TEAE | 19 (14.8)                  | 18 (22.8)                  |
| Instillation site pain     | 10 (7.8)                   | 15 (19.0)                  |
| Eye irritation             | 2 (1.6)                    | 3 (3.8)                    |
| Eye pruritus               | 2 (1.6)                    | 0                          |
| Ocular hyperemia           | 2 (1.6)                    | 1 (1.3)                    |
| Eye pain                   | 1 (0.8)                    | 1 (1.3)                    |
| Eyelid edema               | 1 (0.8)                    | 1 (1.3)                    |
| Chalazion                  | 0                          | 1 (1.3)                    |
| Conjunctivitis allergic    | 0                          | 1 (1.3)                    |
| Lacrimation increased      | 0                          | 1 (1.3)                    |

Values are n (%).

CsA CE = 0.1% (1 mg/mL) cyclosporine A cationic emulsion; SAF = safety analysis set; TEAE = treatment-emergent adverse event.

<sup>a</sup> An adverse event was considered to be a TEAE if the date of onset of the event was on or after the date of the first study drug dose.

site pain, the treatment-related ocular TEAEs reported in at least 1.5% of patients in either group were eye irritation, eye pruritus, and ocular hyperemia (CsA CE/CsA CE group; each in 2 patients [1.6%]) and eye irritation (vehicle/CsA CE group; 3 patients [3.8%]). Considering all treatment-related ocular TEAEs except instillation site pain, there were no clear trends for increased incidence of any treatment-related ocular TEAE in either group.

During part 2, treatment with CsA CE was discontinued due to treatment-related TEAEs in 8 patients (6.3%) in the CsA CE/CsA CE group and 7 (8.9%) in the vehicle/CsA CE group (Tab. III). The most frequently reported treatment-related TEAE leading to permanent discontinuation was instillation site pain, reported in 5 patients (3.9%) in the CsA CE/CsA CE group and 5 (6.3%) in the vehicle/CsA CE group. The severity of this adverse event ranged from mild to severe (mild, 3 patients; moderate, 6 patients; severe, 1 patient), and resolved after discontinuation in all but 3 patients.

Cyclosporine A levels were not available for 45 patients (35.2%) in the CsA CE/CsA CE group and 29 patients (36.7%) in the vehicle/CsA CE group at month 12. Among evaluable patients at month 12, blood sampling revealed that systemic CsA could not be detected in a large proportion (43.8%, CsA CE/CsA CE; 40.5%, vehicle/CsA CE). Cyclosporine A levels could be detected, but not measured (<0.10 ng/mL), in 14.8% of patients in the CsA CE/CsA CE group and 16.5% of patients in the vehicle/CsA CE group. Cyclosporine A was quantifiable, but below the upper limit of quantification (≤5.0 ng/mL) in 7 patients in the CsA CE/CsA CE group and 4 patients in the vehicle/CsA CE group; these levels were considered to be negligible by the investigators. Two patients (1 in each group) showed CsA levels above the upper limit of quantification (>5.0 ng/mL); however, these patients had elevated CsA levels since baseline resulting from treatment with systemic CsA.

## Discussion

A key factor in the pathogenesis of DED is inflammation, and the infiltration of T cells and proinflammatory cytokines into the ocular surface is known to initiate a cascade of events that result in the progression of its signs and symptoms (3). First-line treatments such as artificial tears provide some symptomatic relief; however, they fail to address the underlying cause of the disease, namely inflammation. Without appropriate and adequate treatment, the ocular surface becomes progressively damaged, and DED may exert a profound negative impact on quality of life (18). Topical cyclosporine, an immunomodulatory agent, can effectively inhibit T cells and cell-mediated inflammatory pathways, thus resulting in reduction of the symptoms of DED and restoring the ocular surface (19, 20).

The double-masked phase of the SANSIKA phase III study (part 1) established the efficacy and safety of CsA CE in improving severe keratitis in patients with severe DED (13). The results of the current part 2/OLE phase of the SANSIKA study reiterated the findings of part 1, showing that CsA CE was effective in alleviating signs and symptoms of DED, and also showed that it was capable of maintaining these positive outcomes over a 12-month period. Data for CFS scores indicated that CsA CE continuously improved signs of keratitis for up to 12 months of treatment and substantially improved corneal clearing. Reductions in HLA-DR expression were largely maintained in patients remaining on CsA CE during part 2 of the study, and were more pronounced among those who switched from vehicle to CsA CE in part 2. Cyclosporine A CE was also associated with improvements in global DED symptoms scores (OSDI and VAS), which decreased during the course of the 12-month study. Compliance with the treatment regimens and adherence to the once-daily eyedrop instillation instructions were high over the 12-month study period, presumably because most patients experienced and perceived a positive response to treatment.

Cyclosporine A CE was well-tolerated, and the safety profile of CsA CE in the 6-month OLE was similar to that reported for the part 1 double-masked period (13), with no newly reported events. As expected with a CsA CE treatment, the most frequently reported treatment-related adverse event was instillation site pain. Although inconsequential amounts of systemic CsA were detected in some study patients who were receiving systemic CsA, there were no reports of systemic adverse events.

The favorable safety/tolerability of CsA CE reflected in the overall SANSIKA trial are consistent with the findings of the phase 3 SICCANOVE trial of CsA CE (21). The safety and tolerability of CsA CE also compare favorably with those of other CsA formulations: *in vitro* and *in vivo* data have demonstrated an ocular safety profile for CsA CE comparable to that of Restasis (an anionic CsA 0.05% emulsion) and hospital-compounded CsA formulations (22); moreover, a review of clinical studies of CsA 0.05% emulsions in DED reported an overall safety profile consistent with that shown for CsA CE (23). Because CsA CE is a cationic emulsion, it has greater corneal bioavailability compared with anionic CsA emulsions (10), allowing once-daily dosing (vs multiple times per day for

other CsA formulations), and thus suggesting the potential for greater overall ocular tolerability. Cyclosporine A CE also has the advantage of good manufacturing practices-aligned quality control oversight, which is lacking with hospital-based CsA formulations, thus mitigating concerns over variable concentration and unknown constituents (24).

Limitations of this study include the fact that the analyses were descriptive in nature, as all patients received treatment in the OLE. In addition, concomitant use of AT was permitted, which may have confounded interpretation of CsA CE's effects. However, patients recruited into the SANSIKA study had severe DED and had been refractory to other treatments; hence the positive outcomes observed were unlikely to have been impacted by lubricants used in conjunction with the treatment drug.

In conclusion, in the SANSIKA study, once-daily CsA CE for up to 12 months was well-tolerated and yielded continuous improvements in corneal staining, ocular surface inflammation, and ocular symptoms, suggesting a sustained effect in patients with DED with severe keratitis. Improvements were observed both in those who remained on CsA CE in the OLE segment of the study (indicating the value of treatment beyond 6 months) and in those who switched from vehicle to CsA CE (indicating the benefit of the active component).

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Conflict of interest: C. Baudouin is a consultant for or has received a research grant from Alcon, Allergan, Santen, and Théa, and was an international coordinator in the SANSIKA study. M. Sainz de la Maza was an investigator in the SANSIKA study. M. Amrane, J.S. Garrigue, and D. Ismail are employees of Santen SAS. F.C. Figueiredo is a consultant for Théa and Santen and was an investigator in the SANSIKA study. A. Leonardi is a consultant for or has received a research grant from Alcon, Allergan, Medivis, Santen, Sifi, and Théa, and was an investigator in the SANSIKA study.

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