Persistence of Efficacy of 0.1% Cyclosporin A Cationic Emulsion in Subjects with Severe Keratitis Due to Dry Eye Disease: A Nonrandomized, Open-Label Extension of the SANSIKA Study

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ABSTRACT

Purpose: Results from a 6-month double-masked and a 6-month open-label study (SANSIKA) established the efficacy and safety of once-daily 0.1% cyclosporin A cationic emulsion (CsA CE) in severe keratitis due to dry eye disease (DED). This article presents results from the Post-SANSIKA study, a 24-month extension of SANSIKA assessing the sustained efficacy of CsA CE after treatment discontinuation.

Methods: Time to relapse (corneal fluorescein staining [CFS] score ≥4 [modified Oxford scale]) was assessed after treatment discontinuation in patients from the SANSIKA study who had CFS improvement from a score of 4 to ≤2 after 6 or 12 months of treatment with CsA CE.

Findings: Of 62 patients who achieved a CFS score ≤2 at the end of the SANSIKA study, 38 did not relapse and 24 (39%) relapsed during the 24-month period after CsA CE discontinuation; the latter (relapse) group comprised 35% of patients initially treated with CsA CE for 12 months in SANSIKA versus 47% of those treated for 6 months only. Patients spent the most time during the extension study at CFS scores of 1 or 2 (median duration of 8.5 weeks and 14.7 weeks per year, respectively), indicating marked improvement, and less time at scores of 3, 4, or 5 (median time, 2.0 weeks, 0 weeks, and 0 weeks per year). Of 23 patients eligible for safety analysis (ie, patients who received the study treatment at least once), 12 (52.2%) reported a total of 26 ocular adverse events (AEs). Among these, 5 ocular AEs, reported in 5 patients (21.7%), were considered related to study treatment: 3 events of mild instillation site pain in 3 patients (13.0%) and eye discharge and foreign body sensation, each reported in 1 patient (4.3%). Only 1 systemic AE (nasal congestion), reported in 1 patient (4.3%), was considered related to study treatment. None of the AEs led to treatment discontinuation.

Implications: The majority of patients who discontinued CsA CE after experiencing DED improvement in the SANSIKA study did not experience a relapse in this 24-month follow-up study; these patients spent the most time at CFS scores consistent with marked improvement. CsA CE had a

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favorable safety/tolerability profile over 2 years. Treatment for up to 12 months with CsA CE provides sustained improvements in patients with severe keratitis due to DED. EudraCT registration no. 2012-002066-12. (*Clin Ther*. 2018;40:XXX–XXX) © 2018 Published by Elsevier Inc.

Key words: cationic emulsion, cyclosporin A, dry eye disease, inflammation, keratoconjunctivitis sicca, severe keratitis.

INTRODUCTION

Dry eye disease (DED), characterized by symptoms of discomfort (eg, ocular dryness, pain, burning sensations), visual disturbances, and tear film instability, is a common ocular condition with an estimated worldwide prevalence of 5% to 50% in adults, depending upon the disease definition applied, and with a variable age of onset.[1,2] There are 2 major classes of dry eye—aqueous tear-deficient and evaporative—each with distinct underlying pathophysiologies and extrinsic causes.[3] The mechanisms of DED can overlap and even amplify the severity of the disease, producing a vicious cycle of inflammatory events and ocular surface damage.[4]

Despite substantial clinical research conducted on DED, this multifactorial disease has proven markedly resistant to treatment, particularly in its more severe manifestations. Topical corticosteroids can provide beneficial clinical improvement, but the long-term use of these agents is limited by side effects such as cataracts and intraocular hypertension.[5,6] Artificial tears (more properly termed "ocular lubricants" in most cases) are commonly used to treat the symptoms of DED. However, these agents have not been shown to provide more than short-term symptomatic relief.

Cyclosporin A (CsA) has been shown to have a positive effect on the inflammatory component of DED[7] and to be suitable for long-term therapy.[8,9] Hospital-compounded formulations of CsA are commonly used to treat DED in the European Union; however, absence of a Good Manufacturing Practice–aligned process for such formulations raises concerns regarding standardization of the manufacturing operation and quality control of these products.[10] An anionic oil-in-water emulsion incorporating CsA 0.05%* was approved by the US Food and Drug Administration in 2003 to increase tear production in patients with keratoconjunctivitis sicca.[11] Because CsA is a lipophilic drug, a formulation was developed in a cationic emulsion (CE) containing unpreserved 0.1% (1 mg/mL) CsA (CsA CE)† to help improve its retention on the surface of the eye and increase its bioavailability.[12,13] CsA CE was registered in 2015 in the European Union for the treatment of severe keratitis in adult patients with DED that has not improved despite treatment with tear substitutes.[14]

The efficacy and safety of CsA CE have been documented in 2 randomized, vehicle-controlled, 6-month, Phase III studies: SANSIKA in patients with severe DED[15] and SICCANOVE in patients with moderate to severe DED.[16] In addition, findings from a subsequent 6-month, open-label extension of SANSIKA suggest that it is well tolerated and yields continuous improvements in signs and symptoms of DED for up to 12 months.[17] The present article reports results from the Post-SANSIKA study, a 2-year, open-label, nonrandomized extension of the SANSIKA Phase III study, which was designed to assess the sustained efficacy of CsA CE after discontinuation of treatment in patients who had previously received either 6 or 12 months of CsA CE therapy in the previous 2 segments of the study.

PATIENTS AND METHODS

SANSIKA Part 1/Part 2 Study Design

As previously described,[15] SANSIKA enrolled patients aged ≥18 years with severe DED. All patients had a corneal fluorescein staining (CFS) score of 4 on a 7-point (0, 0.5, 1–5) modified Oxford scale[18]; a Schirmer's test score ≥2 mm/5 min and <10 mm/5 min[3]; and an Ocular Surface Disease Index score ≥23.[19] The study included 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).[15,17] It was conducted at 50 centers in France, Germany, Italy, Spain, Belgium, United Kingdom, Sweden, Austria, and the Czech Republic. In Part 1,

* Trademark: Restasis® (Allergan, Inc, Irvine, California).

† Trademark: Ikervis® (Santen SAS, Evry, France).

patients were randomized to receive 1 drop once daily at bedtime of CsA CE or vehicle. In Part 2, all patients received CsA CE on the same once-daily schedule. Thus, Part 2 included patients who continued on CsA CE after receiving it for 6 months in Part 1 (CsA CE/CsA CE group) and patients who had received vehicle for 6 months and were then switched to CsA CE (vehicle/CsA CE group).[15,17]

Efficacy assessments in SANSIKA included objective parameters (signs) such as CFS, Schirmer's test (without anesthesia), lissamine green conjunctival staining, and tear break-up time, as well as subjective (symptoms) parameters such as the Ocular Surface Disease Index, a visual analog scale (VAS) of ocular discomfort, the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), and the use of concomitant artificial tears.[15] Safety assessments included best-corrected distance visual acuity in both eyes, intraocular pressure in both eyes, blood sampling for CsA levels, vital signs (blood pressure, pulse, and respiratory rates), ocular and systemic adverse events (AEs), and slit-lamp examination of both eyes.

Post-SANSIKA Study Design

Upon completion of the SANSIKA main study (month 12 visit), patients were invited to enter the 24-month, prespecified extension study (Post-SANSIKA), during which they received CsA CE treatment (1 drop once daily at bedtime) or no treatment, depending on their clinical condition (Figure 1). Only patients who had received active treatment (CsA CE) during at least the last 6 months of the SANSIKA study and who had a CFS score ≤ 3 on at least 1 visit during Part 2 (whether it was at a planned or an unscheduled visit) were included in the extension study, which was conducted between October 2012 and October 2014. Of the 177 patients who completed SANSIKA, 110 patients were not included in the extension study due to the following reasons: many patients (n = 64) were not offered the option to participate in the current extension study because the month 12 visit of SANSIKA occurred before all regulatory approvals were obtained for the extension study; some clinical centers declined to participate in the extension study (n = 15 patients); 29 patients refused to enter the Post-SANSIKA study; and 2 patients were not eligible due to nonimprovement after CsA CE treatment at the end of the SANSIKA study period.

CFS was assessed by using the modified Oxford scale, and the eye with the maximal CFS score ("worst eye," defined at each visit) was used for analysis. CsA CE was discontinued if patients had a CFS score ≤ 2 and restarted if the score was ≥ 4 (relapse). Treatment was permanently discontinued if the CFS score was ≥ 4 for 6 months. The 24-month extension study comprised a total of 10 visits, held at month 12 (study entry, which was the last visit of the main study), month 13, month 15, and then every 3 months or at the patient's request. Throughout all phases of SANSIKA and the current 24-month extension, patients were allowed to use unpreserved, sponsor-provided artificial tears (saline solution)[‡]; no other rescue medications were permitted.

All enrolled patients provided written informed consent, and the study was conducted in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki. This study was registered in the EudraCT database (2012-002066-12) with the protocol code number NVG12D122.

Study Populations

The targeted population of the Post-SANSIKA extension study consisted of all patients who completed the SANSIKA main study, excluding treatment-resistant patients (patients who did not experience improvement in CFS score [ie, patients with a CFS score ≥ 4 for the worst eye] at months 9 and 12 of the main study). The targeted population therefore corresponded to patients with severe DED who were not treatment resistant. Four populations were considered for analysis: the primary efficacy, the secondary efficacy, the "full" population, and safety.

The primary efficacy population consisted of all patients who were eligible for the Post-SANSIKA extension study and had an improvement in CFS score from 4 to ≤ 2 at month 12 of SANSIKA Part 2 (ie, after 6 or 12 months of treatment with CsA CE in the SANSIKA study) or at any time during the 24-month follow-up period. This population, which was designated as "markedly improved patients," was used for the analysis of the primary efficacy end point and some secondary analyses.

‡ Trademark: Larmabak® (Théa, Clermont-Ferrand, France).

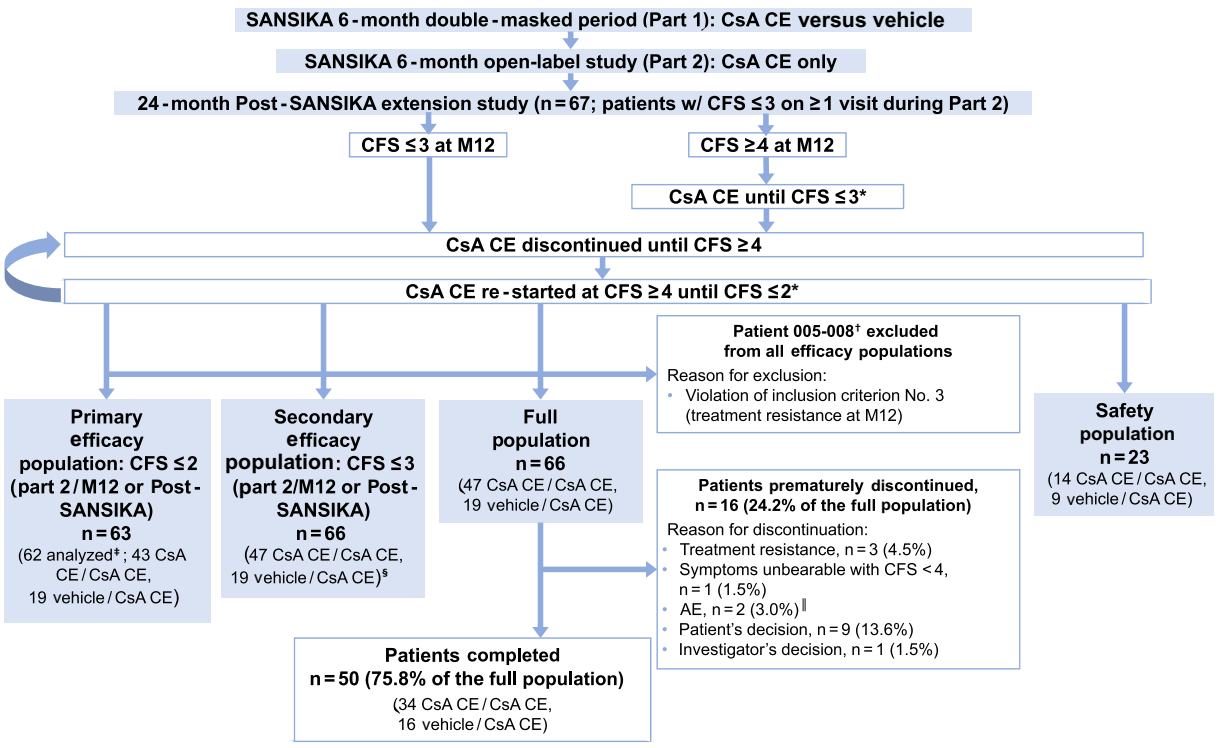

Figure 1. Study design and patient flow for the Post-SANSIKA extension study. *Treatment was permanently discontinued if the corneal fluorescein staining (CFS) score was ≥4 for 6 months. †Patient 005-008 was excluded from the primary and secondary efficacy populations and the full population but was included in the safety population. ‡For Patient 312-007, time to relapse could not be calculated due to the use of prohibited concomitant medication before the first CFS assessment during the extension study. §Fifty-four patients (39 cyclosporin A 0.1% [1 mg/mL] cationic emulsion [CsA CE]/CsA CE, 15 vehicle/CsA CE) of 66 were included in the time to relapse analyses; for the remaining 12 patients, time to relapse could not be calculated because treatment was never resumed (n = 11), or because prohibited concomitant medication was used before treatment was resumed (n = 1). ‖Patients 311-001 and 801-002 were discontinued due to an adverse event (AE); however, these 2 patients were not included in the safety population because they never took study medication during the extension study. The CsA CE/CsA CE group received 12 months of CsA CE treatment during SANSIKA Parts 1 and 2 (ie, before the current extension study); the vehicle/CsA CE group received 6 months of CsA CE treatment during this time frame. The primary efficacy population included patients with marked CFS improvement (from scores 4 to ≤2 after 6 or 12 months of treatment with CsA CE in the SANSIKA study); the secondary efficacy population included patients with CFS improvement from scores 4 to ≤3 after 6 or 12 months of treatment with CsA CE in the SANSIKA study. M = month.

The secondary efficacy population consisted of all patients who were eligible for the Post-SANSIKA extension study and had achieved a CFS score ≤3 at month 12 of SANSIKA Part 2 (ie, after 6 or 12 months of treatment with CsA CE in the SANSIKA study) or at any time during the 24-month follow-up period. This population was designated as "improved patients."

The "full" population consisted of all patients who participated in the Post-SANSIKA extension study (ie, all patients who gave their informed consent). This population corresponded to all improved or

nonimproved patients who were not treatment resistant at the completion of the SANSIKA study.

The safety population consisted of all patients who participated in the Post-SANSIKA extension study and instilled at least 1 drop of study medication during the extension study.

Study Assessments and End Points

The primary end point of the Post-SANSIKA extension study was duration of improvement (time to relapse) after treatment discontinuation in markedly improved patients (ie, the primary efficacy population). Time to relapse was defined as time from CsA CE discontinuation due to CFS score improvement to CsA CE resumption due to a CFS score $\geq$4.

Secondary end points included the following: duration of improvement/time to relapse for improved patients (ie, the secondary efficacy population); potential prognostic factors for duration of improvement/time to relapse (subject characteristics, disease characteristics, main study group, mean CFS score over the last 6 months of treatment before CsA CE discontinuation, CFS score at treatment discontinuation [considered as a quantitative variable]) (secondary efficacy population); interrelationships between duration of improvement/time to relapse and determinant factors (quantity of CsA CE used per month, time spent on each CFS score per year, total time spent without treatment, total time spent with treatment, main study group, duration of improvement/time to relapse without CsA CE [from first CFS score $\leq$2 or 3], age, time since diagnosis, presence of Sjögren's syndrome, sex, and premature study discontinuation) (primary efficacy and full populations); time spent at each CFS score per year (primary efficacy, secondary efficacy, and full populations); and time to onset of action of CsA CE (primary efficacy population).

Other secondary end points (not based on CFS assessment) included the following: global VAS assessment (0%−100%), NEI-VFQ-25 composite score, EuroQol 5D Questionnaire (EQ-5D) scores (Summary Index and VAS), tear break-up time, lissamine green total score, and Schirmer's test score (primary efficacy and full populations). Exploratory analyses included: time without treatment, starting at the month 12 visit; sum of the periods during which the patient was not treated, starting after a period of treatment; period during which the patient had dropped out for whatever reason; and sum of the periods during which the patient was treated (full population).

Statistical Analyses

Time-to-event variables were analyzed by using Kaplan-Meier survival analyses. Estimates of median survival times, quartiles and their log-transformed 95% CIs, as well as estimates of mean survival times and associated SEs, were derived. A regression model was used to test for potential prognostic factors that predicted duration of the improvement and interrelationships between duration of improvement/time to relapse and determinant factors.

For some end points, the main study groups (vehicle/CsA CE versus CsA CE/CsA CE) were compared to account for the difference between patients who had been treated with CsA CE for 6 months versus 12 months, respectively, at entry into the extension study. Specifically, time to relapse was compared between the 2 main study groups by using a log-rank test. Other efficacy-related statistics were descriptive, except for the global VAS assessment and EQ-5D and NEI-VFQ-25 questionnaire results, for which time points were compared by using a Wilcoxon test, and several other variables, for which inferential statistics in the form of 95% CIs were calculated. The safety and tolerability of CsA CE and the exploratory end points were descriptively summarized.

RESULTS

Patient Demographic Characteristics and Disposition

Of the 67 patients analyzed, 1 patient did not meet inclusion criteria for CFS assessments but was included in safety analyses (Figure 1). The full population thus included 66 patients (47 in the CsA CE/CsA CE group and 19 in the vehicle/CsA CE group; 87.9% female), and 50 of these (75.8%) completed the extension study (34 in the CsA CE/CsA CE group and 16 in the vehicle/CsA CE group). For the 16 patients (24.2%) who dropped out before month 36, the reasons for discontinuation were patient's decision (n = 9; 13.6% of full population), treatment resistance (n = 3; 4.5%), AE (n = 2; 3.0%), symptoms unbearable with CFS score <4 (n = 1; 1.5%), and investigator's decision (n = 1; 1.5%). Baseline characteristics of the full population are listed in Table I.

Table I. Patient demographic characteristics (full population).

Characteristic	Full Population (N = 66)
Age	
Mean (SD) age, y	61.1 (12.9)
Range (min; max)	24.1; 81.1
Sex, no. (%)	
Female	58 (87.9)
Male	8 (12.1)
Sjögren's syndrome, no. (%)	28 (42.4)
Time since diagnosis, y	
Mean (SD)	9.93 (7.13)
Range (min; max)	1.3; 31.9

max = maximum; min = minimum.

Efficacy Results

Primary End Point: Time to Relapse in Markedly Improved Patients

In the primary efficacy population (n = 63), 62 patients who discontinued treatment due to a CFS score ≤2 were analyzed (43 CsA CE/CsA CE patients and 19 vehicle/CsA CE patients) (Figure 1). Of these 62 markedly improved patients, 24 patients (38.7%) experienced a relapse (15 patients [34.9%] in the CsA CE/CsA CE group and 9 patients [47.4%] in the vehicle/CsA CE group) (Figure 2). Based on the first quartile (the median could not be estimated due to the small number of relapses), 25% of the patients who received CsA CE for 12 months (CsA CE/CsA CE) had a relapse within 224 days (95% CI, 113–not evaluable), which corresponds to a time to relapse of 32 weeks (~7.4 months). By comparison, relapse occurred within 175 days (95% CI, 28–not evaluable) in the first quartile of patients who received CsA CE for 6 months (vehicle/CsA CE) (P =

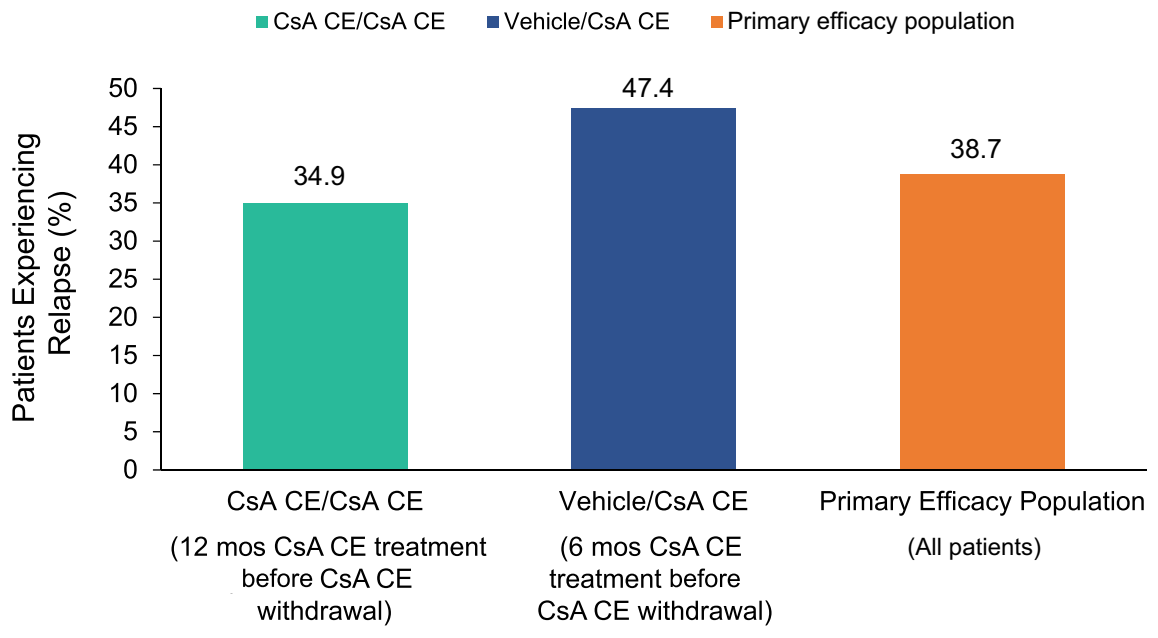

Figure 2. Relapse (corneal fluorescein staining [CFS] score ≥4) in markedly improved patients (those with CFS score improvement from score 4 to ≤2 [modified Oxford scale] after 6 or 12 months of treatment with cyclosporin A 0.1% [1 mg/mL] cationic emulsion [CsA CE]). The CsA CE/CsA CE group received 12 months of CsA CE treatment during SANSIKA Parts 1 and 2 (ie, before the current extension study); the vehicle/CsA CE group received 6 months of CsA treatment during this time frame. mos = months.

0.491), which corresponds to a time to relapse of 25 weeks (~5.5 months). A Kaplan-Meier analysis of time to relapse after 6 or 12 months of treatment with CsA CE is shown in Figure 3.

Time to Relapse in Improved Patients

In the secondary efficacy population (n = 66), 54 patients who discontinued treatment due to a CFS score ≤3 were analyzed; 30 patients (55.6%) did not experience a relapse, and 24 patients experienced a relapse (44.4%). Based on the first quartile (as with the primary efficacy analysis, the median could not be estimated due to the small number of relapses), 25% of improved patients had a relapse within 175 days (95% CI, 89−284), which corresponds to a time to relapse of 25 weeks (~5.5 months).

Prognostic Factors for Time to Relapse After Treatment Discontinuation

No variables were identified as prognostic factors for time to relapse in the secondary efficacy population using the regression model, either at the 5% or 10% level of significance. The variables analyzed were subject characteristics (age and sex), disease characteristics (duration of the disease and presence of Sjögren's syndrome), main study group, mean CFS score over the last 6 months of treatment before treatment discontinuation, and CFS score at treatment discontinuation.

Interrelationships Between Determinant Factors and Time to Relapse

Analysis of determinant factors for time to relapse in the primary efficacy population found that 1 factor (driven by variables related to duration of treatment and disease severity) explained 35% of the total variance. The number of days per month on treatment, the number of weeks per year at a CFS score ≥4, and the number of weeks per year at a CFS score of 3 correlated positively with this factor, whereas time to relapse in improved patients, days without treatment, and number of weeks per year at a CFS score ≤0.5 correlated negatively.

A second factor (driven by variables related to patient characteristics) explained 19% of total variance: female sex, presence of Sjögren's syndrome, and age correlated positively with the second factor, whereas number of weeks per year at a CFS score of 1 correlated negatively. Similar results were seen in the full population.

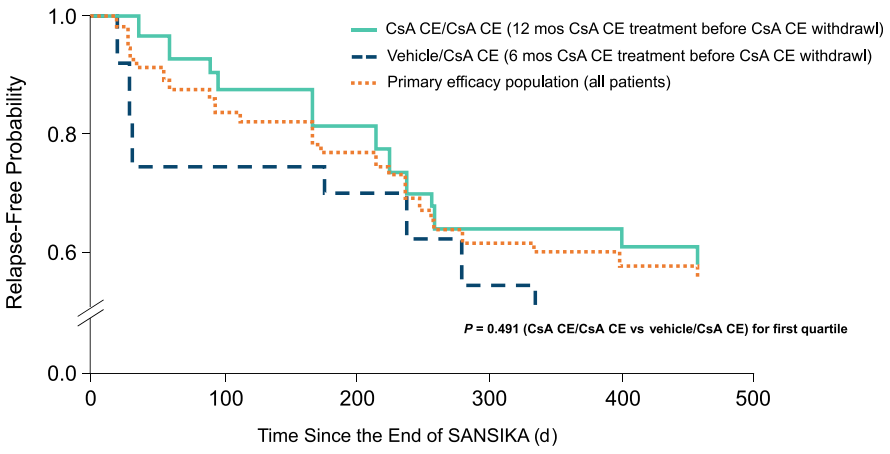

Figure 3. Kaplan-Meier curve of the time to relapse in markedly improved patients (primary efficacy population). Based on the first quartile, 25% of markedly improved patients (those with corneal fluorescein staining score improvement from 4 to ≤2 [modified Oxford scale] after 6 or 12 months of treatment with cyclosporin A 0.1% [1 mg/mL] cationic emulsion [CsA CE]) had a relapse within 224 days (95% CI, 113−333), which corresponds to a time to relapse of 32 weeks. The CsA CE/CsA CE group received 12 months of CsA CE treatment during SANSIKA Parts 1 and 2 (ie, before the current extension study); the vehicle/CsA CE group received 6 months of CsA CE treatment during this time frame. d = days; mos = months.

Time Spent at Each CFS Score

In the primary efficacy population, patients spent the most time at CFS scores of 1 or 2 (median time, 8.5 weeks and 14.7 weeks per year, respectively), and relatively less time at CFS scores of 3, 4, or 5 (median time, 2.0 weeks, 0 weeks, and 0 weeks per year) (Table II). These results are consistent with the finding that most patients did not experience a relapse during the extension study. The CFS score at which patients spent the most time during the

Table II. Time spent at each corneal fluorescein staining (CFS) score per year (weeks) (primary efficacy population).

CFS Score	Treatment Group		Total Population (N = 63)
	CsA CE/CsA CE (12 mos CsA CE treatment before CsA CE withdrawal) (n = 44)	Vehicle/CsA CE (6 mos CsA CE treatment before CsA CE withdrawal) (n = 19)	
CFS = 0			
Mean (SD)	8.44 (15.29)	3.44 (9.89)	6.93 (14.00)
Median (Q1; Q3)	0.00 (0.0; 9.4)	0.00 (0.0; 0.2)	0.00 (0.0; 4.4)
Range (min; max)	(0.0; 52.0)	(0.0; 41.6)	(0.0; 52.0)
CFS = 0.5			
Mean (SD)	3.88 (6.87)	2.04 (4.18)	3.33 (6.21)
Median (Q1; Q3)	0.00 (0.0; 5.8)	0.00 (0.0; 2.4)	0.00 (0.0; 5.4)
Range (min; max)	(0.0; 27.4)	(0.0; 15.9)	(0.0; 27.4)
CFS = 1			
Mean (SD)	11.54 (12.93)	13.93 (17.83)	12.26 (14.47)
Median (Q1; Q3)	8.53 (0.0; 18.3)	1.96 (0.0; 25.5)	8.52 (0.0; 24.0)
Range (min; max)	(0.0; 52.0)	(0.0; 52.0)	(0.0; 52.0)
CFS = 2			
Mean (SD)	17.28 (16.03)	18.48 (17.60)	17.64 (16.38)
Median (Q1; Q3)	14.42 (2.8; 27.2)	14.74 (1.6; 28.8)	14.74 (1.9; 27.7)
Range (min; max)	(0; 50.0)	(0.0; 52.0)	(0.0; 52.0)
CFS = 3			
Mean (SD)	8.87 (12.76)	7.90 (11.35)	8.58 (12.27)
Median (Q1; Q3)	2.81 (0.0; 16.2)	1.61 (0.0; 14.8)	2.03 (0.0; 14.8)
Range (min; max)	(0.0; 48.2)	(0.0; 39.7)	(0.0; 48.2)
CFS = 4			
Mean (SD)	2.00 (4.33)	5.93 (11.98)	3.19 (7.61)
Median (Q1; Q3)	0.00 (0.0; 0.0)	0.00 (0.0; 5.2)	0.00 (0.0; 4.3)
Range (min; max)	(0.0; 18.2)	(0.0; 48.8)	(0.0; 48.8)
CFS = 5			
Mean (SD)	0.00 (0.00)	0.27 (0.86)	0.08 (0.48)
Median (Q1; Q3)	0.00 (0.0; 0.0)	0.00 (0.0; 0.0)	0.00 (0.0; 0.0)
Range (min; max)	(0.0; 0.0)	(0.0; 3.5)	(0.0; 3.5)

CsA CE = cyclosporin A 0.1% (1 mg/mL) cationic emulsion; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile.
Note: The CsA CE/CsA CE group received 12 months of CsA CE treatment during SANSIKA Parts 1 and 2 (ie, before the current extension study); the vehicle/CsA CE group received 6 months of CsA treatment during this time frame. mos = months.

extension study was 2, which was categorized as a marked improvement. Patients who were treated with CsA CE for 12 months during the main study tended to spend more time with a CFS score of 1 than patients treated for 6 months (median time, 8.5 versus 2.0 weeks per year). Differences for other scores were minor. These results were confirmed in the secondary efficacy population and the full population (data not shown).

Time to Onset of Action of CsA CE

Onset of action of CsA CE treatment in the primary efficacy population was detected within 168 days (24 weeks) in 50% of the patients (95% CI, 138−410).

Other Secondary Analyses

From the time treatment was first stopped to the time it was restarted, all symptoms of ocular discomfort assessed according to the VAS worsened, except for ocular pain, which remained relatively stable. In the full population, the median increase in symptoms over time ranged from 3.0 to 16.0 (on a scale of 0% to 100%) and was statistically significant for foreign body sensation (6.0; $P = 0.028$) and eye dryness (16.0; $P = 0.026$). The median global VAS score, despite increasing from the time treatment was first stopped (23.3%) to the time treatment was restarted (45.1%), remained <50%. Similar trends were found in the primary efficacy population; the increase in symptoms over time was statistically significant not only for foreign body sensation (10.5; $P = 0.013$) and eye dryness (31.0; $P = 0.011$) but also for itching (7.0; $P = 0.032$). Throughout the study, patients were allowed to use unpreserved sponsor-provided artificial tears (saline solution) as needed for the relief of their symptoms of DED. The use of artificial tears was monitored over the course of the study for each patient. Unfortunately, although all 66 patients from the full population returned bottles of artificial tears (used or unused) at some stage during the study, they did not necessarily do so in a systematic fashion. Consequently, the use of artificial tears was difficult to analyze due to missing data.

The composite score of the NEI-VFQ-25 questionnaire in the full population tended to decrease from the time treatment was first stopped to the time it was restarted (median change, −3.5 points), indicating a slight decrease in vision-related quality of life. However, interpretation of these results was hampered by missing data. Similar trends were observed in the primary efficacy population (data not shown).

For the EQ-5D questionnaire, both the Summary Index and the VAS score did not show major changes from the time treatment was first stopped to the time it was restarted in the full population. However, interpretation of these results was hampered by missing data. Similar trends were observed in the primary efficacy population (data not shown).

Other ocular assessments did not indicate any major changes over the duration of the extension study. Between month 12 and month 36, median values in the full population changed from 4 to 5 seconds for tear break-up time, from 1.5 to 1.0 points for lissamine green total score, and from 5.0 to 4.0 mm/5 min for the Schirmer's test score. Similar results for these 3 parameters were found in the primary efficacy population (data not shown). These data must be considered with caution, as they were only available for a small number of patients.

Exploratory Analyses of the Treatment Periods (Full Population)

After the month 12 visit, 25% of patients spent ≤98 days per year without treatment other than artificial tears (ie, 14 weeks, based on the first quartile), whereas 50% of patients spent 336 days per year without treatment (48 weeks, based on the median and the maximal values). After a period of treatment with CsA CE, the time without treatment varied markedly between patients, ranging from 0 to 314 days per year. The number of days per year during which patients were treated also varied, ranging from 0 to 297 days.

Treatment Exposure and Safety

Of the 67 patients enrolled, only 23 (34.3%) received CsA CE treatment at least once during the extension study and were therefore included in the safety analysis. Over the 24-month extension study (~730 days), instillation was performed on a mean of 203 days (range, 35−524 days). Treatment exposure (mean [SD]) was 230 (149) days in the CsA CE/CsA CE group (n = 14) and 170 (118) days in the vehicle/CsA CE group (n = 9).

Overall, 26 ocular treatment-emergent AEs were reported in 12 patients (52.2%), and 21 systemic AEs were reported in 11 patients (47.8%) (Table III). The

Table III. Summary of treatment-emergent adverse events (AEs).

AE	Safety Population (N = 23)	
	Patients, No. (%)	Events, No.
Ocular AEs		
Any ocular AE	12 (52.2)	26
Any treatment-related ocular AE	5 (21.7)	5
Any treatment-related ocular AE upon instillation	3 (13.0)	3
Any ocular serious AE	1 (4.3)	2
Any ocular AE leading to discontinuation	0	0
Systemic AEs		
Any systemic AE	11 (47.8)	21
Any treatment-related systemic AE	1 (4.3)	1
Any systemic serious AE	5 (21.7)	5
Any systemic AE leading to discontinuation	0	0
Deaths	0	0

Note: A study-emergent AE was defined as an event that started on or after the date of the final (month 12) visit of the main SANSIKA study.

Table IV. Incidence of treatment-emergent treatment-related adverse events (AEs).

AE	Safety Population (N = 23)	
	Patients, No. (%)	Events, No.
Any related ocular AE	5 (21.7)	5
Eye disorders		
Eye discharge	1 (4.3)	1
Foreign body sensation in eyes	1 (4.3)	1
General disorders and administration site conditions		
Instillation site pain	3 (13.0)	3
Any related systemic AE	1 (4.3)	1
Respiratory, thoracic, and mediastinal disorders		
Nasal congestion	1 (4.3)	1

Note: A study-emergent AE was defined as an event that started on or after the date of the final (month 12) visit of the main SANSIKA study.

most commonly reported treatment-emergent ocular AEs (data not shown) were foreign body sensation and instillation site pain, each reported in 3 patients (13.0%). The other treatment-emergent ocular AEs reported in >1 patient were eye discharge, reduced visual acuity, and viral conjunctivitis, each reported in 2 patients (8.7%). A total of 5 ocular treatment-emergent AEs, reported in 5 patients (21.7%), were considered related to study treatment (Table IV). These included mild instillation site pain (3 patients [13.0%]), eye discharge (1 patient [4.3%]), and foreign body sensation in the eyes (1 patient [4.3%]).

There were 7 serious adverse events (SAEs): 2 ocular SAEs reported in 1 patient (4.3%) and 5 systemic SAEs reported in 5 patients (21.7%). No SAE was deemed to be related to treatment. Among the SAEs reported, only 3 events occurred during a period of CsA CE treatment: 2 ocular SAEs in 1 patient (high intraocular pressure and decreased visual acuity) and 1 systemic SAE in 1 patient (ankle fracture). Only 2 AEs were classified as severe, both systemic (acute myocardial infarction and lumbar spinal stenosis), and neither was deemed to be related to the study drug. One systemic AE (nasal congestion), reported in 1 patient (4.3%), was seen with each instillation and was considered "probably" related to study treatment. None of the AEs led to study discontinuation.

DISCUSSION

The primary objective of this Post-SANSIKA study was to assess the sustainability of the effect of CsA CE after treatment discontinuation in patients who had CFS score improvement during the SANSIKA study. The majority of patients (61.3%) with prior CFS score improvement from 4 to ≤2 did not relapse (return to a CFS score ≥4) during the current 2-year extension study; in addition, more than one half (55.6%) of patients with previous improvement from a CFS

score of 4 to ≤3 did not relapse. Furthermore, patients spent the most time at CFS scores of 1 or 2, indicating a marked improvement (median time of 8.5 weeks and 14.7 weeks per year, respectively), and relatively less time at CFS scores of 3, 4, or 5 (median time, 2.0 weeks, 0 weeks, and 0 weeks per year).

Treatment differences between patients who had received CsA CE for 12 months versus 6 months during the main study were observed. Patients in the CsA CE/CsA CE group, who received treatment for 12 months before the extension study, were less likely to relapse than those treated for only 6 months (35% versus 47%, respectively), and these patients also spent more time at a CFS score of 1 (median time, 8.5 versus 2.0 weeks per year).

With respect to secondary analyses not based on CFS assessments, VAS scores in the present study showed a worsening of patients' discomfort from the time treatment was first stopped to the time it was restarted. All items of ocular discomfort except pain worsened during that time frame, although the median global VAS score remained below 50 (increasing from 23.3% at the time treatment was first stopped to 45.1% at the time it was restarted). Other ocular and quality of life assessments did not exhibit major changes over the duration of the extension study (with the exception of a small decrease in NEI-VFQ-25 scores between the time treatment was first stopped and the time it was restarted, indicating a slight decrease in vision-related quality of life). The lack of correlation between these measures related to DED symptoms and those related to CFS scores is not surprising given the well-established discordance between DED signs and symptoms.[20]

A regression analysis failed to reveal prognostic variables associated with duration of improvement (time to relapse). In a multivariate analysis (principal components analysis), 2 factors—one driven by variables linked to duration of treatment and disease severity, the other by variables linked to patient characteristics—were identified that explained 35% and 19%, respectively, of the total variance in the time-to-relapse data in our study. The first factor correlated positively with patients' length of treatment and the length of time for which they had a CFS score ≥3; the second correlated with characteristics known to be associated with more severe DED (patient age, female sex, and presence of Sjögren's syndrome).

CsA CE was found to be well tolerated over the 24-month duration of this study, and no new safety events were noted compared with those identified in the 2 previous segments of the SANSIKA study or the SICCANOVE study.[15–17] The most commonly reported treatment-related AE was instillation site pain; this event is expected with CsA treatment. It is worth noting that instillation site pain was reported in 13% of patients in the current study, a substantially lower incidence than that seen in CsA CE patients in SANSIKA Part 1 (29%), suggesting that, over time, this event may resolve in some individuals. No AEs led to study discontinuation.

One limitation of the current study was that all patients were allowed treatment with artificial tears, which potentially confounded interpretation of the results. However, it would not have been ethical to prohibit the use of lubricant eye drops in this population with severe DED; in addition, because this use was limited to a simple saline solution, we assume that it had only a marginal influence on CFS score improvement in this population. In fact, it is likely that use of saline solution eye drops alone might have predisposed patients to more CFS recurrences compared with a "real-life" scenario in which more efficient lubricants than simple saline solution might be used. Another limitation is that the Post-SANSIKA extension study population was relatively small (N = 66, full population) compared with the number of patients randomized in the initial segment of the main SANSIKA study (N = 246).[15] As noted previously, many patients were not offered the option to participate in the current extension study because of a delay between completion of Part 2 of the SANSIKA study and required regulatory approvals for the extension (Post-SANSIKA) study.

CONCLUSIONS

Results from the Post-SANSIKA 2-year extension study showed maintenance of global improvement in the patients' condition after discontinuation of CsA CE treatment. The majority of patients did not experience a relapse, and most of the patients' time was spent at CFS scores consistent with marked improvement. It was also observed that patients who were treated for longer periods were less likely to

relapse. Overall, CsA CE exhibited a favorable safety and tolerability profile. The findings of this study suggest that continued treatment with CsA CE may provide sustained improvements in patients with severe keratitis due to DED.

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CONFLICTS OF INTEREST

Dr. Labetoulle is an occasional consultant for Alcon, Allergan, Bausch and Lomb, Dompè, MSD, Novartis, Santen, Shire, and Théa; and was an investigator in the SICCANOVE and SANSIKA studies. Dr. Leonardi is a consultant for Santen; reports lecture fees for Alcon, Allergan, Medivis, and Théa; and was an investigator in the SICCANOVE, SANSIKA, and VEKTIS studies. The VEKTIS study was not previously cited in the article (the findings for this study are currently under consideration for publication). Dr. Baudouin 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. Dr. Garhöfer is a consultant for Allergan, Croma, Santen, and Théa; and was an investigator in the SANSIKA study. Dr. Sainz de la Maza is a consultant for Santen; reports lecture fees for Alcon, Allergan, and Santen; and was an investigator in the SICCANOVE and SANSIKA studies. Dr. Amrane, Ms. Ismail, and Dr. Garrigue are employees of Santen SAS. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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