Clinical Study Report Synopsis

Drug Substance	ciclosporin
Study Code	NVG10E117
Date	31 October 2013
EudraCT Number	2011-000160-97

(SANSIKA): A multicentre, randomised, double-masked, 2 parallel arm, vehicle-controlled, 6-month Phase III trial with a 6-month open label treatment safety follow-up period to evaluate the efficacy and safety of CYCLOKAT® 1 mg/mL (ciclosporin/cyclosporine) eye drops, emulsion administered once daily in adult patients with severe dry eye disease (DED).

Study dates: First subject enrolled: 31 March 2011
Last subject last visit: 13 February 2013

Phase of development: III

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

A total of 50 centres recruited patients during the study. The number of centres that recruited patients per country was: 22 sites in France, 11 sites in Germany, 12 sites in Italy, 14 sites in Spain, 3 sites in Belgium, 1 site in the UK, 1 site in Sweden, 2 sites in Austria, and 1 site in Czech Republic.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Objectives and outcome variables

Co-primary objectives:	**Primary outcome variables:**
To demonstrate the superiority of NOVA22007 1 mg/mL (ciclosporin/cyclosporine [CsA]) eye drops, emulsion over vehicle administered once daily in patients with severe DED after 6 months of treatment (Month 6).	Corneal fluorescein staining-Ocular surface disease index (CFS-OSDI) responder rate A responder was defined as a patient satisfying the following: an improvement of ≥2 points from baseline in CFS (i.e. change in CFS≤-2), and an improvement by ≥ 30% from baseline in OSDI (i.e. % change ≤-30%).
Secondary (safety) objective:	**Safety variables**
To evaluate the ocular tolerability and overall ocular safety of NOVA22007 administered once daily in patients with severe DED over 12 months at 2 time points: at Month 6, after the randomised, double-masked study treatment period and at Month 12, after the open label safety treatment follow-up period	Best corrected distance visual acuity (BCDVA) and intraocular pressure (IOP) in both eyes; blood sampling for CsA levels; vital signs (blood pressures, pulse rate and respiratory rate); ocular/systemic adverse events (AEs); slit lamp examination of both eyes.
Secondary efficacy objectives:	**Secondary outcome variables:**
To further assess the efficacy of NOVA22007 measured by CFS, OSDI, visual assessment scale (VAS) of ocular discomfort, Schirmer test (without anaesthesia) in the analysed eye, and use of concomitant artificial tears (AT) and investigator's global evaluation of efficacy.	CFS, OSDI, VAS and CFS-VAS responder rates; complete corneal clearing. CFS, OSDI, global VAS, and lissamine green total score. Schirmer test; use of concomitant AT.
Other secondary objectives:	**Other secondary variables:**
To further assess the effects of NOVA22007 in the analysis eye, measured by human leukocyte antigens DR (HLA-DR) expression, Tear break up time (TBUT), Lissamine green staining, and tear film osmolarity.	HLA-DR expression; TBUT; Lissamine green staining; Tear film osmolarity (in a subset of patients).
To investigate the effects of NOVA22007 on health-related quality of life using the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) and the EuroQoL 5D Questionnaire (EQ-5D)	NEI-VFQ-25; EuroQoL-5D.

Study design

This was a 6-month, multi-centre, randomised, double-masked, vehicle-controlled (Part 1), parallel group study, with a 6-month open label follow up period (Part 2) to assess the superiority of NOVA22007 over its vehicle, chosen as control.

The study entry criteria were designed to include DED patients with a severe keratitis. Eligible adult patients were to include those with persistent severe DED defined as CFS

graded 4 on the modified Oxford scale, with a Schirmer test score ≥2 mm/5 min and <10 mm/5 min, and the OSDI scored ≥23.

Patients were to be randomised to receive NOVA22007 one drop once daily at bedtime, or its vehicle. Patients randomised to the vehicle group were switched to NOVA22007 after 6 months. Throughout the study, patients attended 7 visits:

- 5 visits during Part 1: Screening Visit (Day -14 to -7), Baseline Visit (Day 0), Month 1 Visit (Day 28 ±3 days), Month 3 Visit (Day 84 ±7 days) and Month 6 Visit (Day 168 ±14 days);
- 2 visits during Part 2: Month 9 Visit (Day 252 ±14 days) and Month 12 Visit (Day 336 ±14 days).

Efficacy was to be only determined in the "analysis eye", which was defined as the worst eligible eye, i.e. the eligible eye with the higher lissamine green staining score at baseline. If both eyes were eligible and had the same lissamine green staining score at baseline, the eye with the worse Schirmer test score at baseline was used. If both eyes had the same Schirmer test score at baseline, the right eye was used. The same eye (eligible eye) had to fulfill all the applicable aforementioned selection criteria.

Patients were to be assessed for signs and symptoms, and for safety. During the study, safety findings were closely monitored on an ongoing basis.

Target subject population and sample size

The target population was male and female DED patients aged 18 and over, with severe keratitis that was not improving despite treatment with lachrymal substitutes.

In total, it was planned to randomise up to 300 patients, to ensure that approximately 250 patients (approximately 168 in the active group and 84 in the control group) received their randomised treatment in the study.

Based on the data of the Phase III study NVG06C103 in moderate to severe DED patients, a sample size of approximately 225 evaluable patients (150 in the active group and 75 in the vehicle group, according a 2:1 ratio) was to provide at least 90% power to detect a difference (between NOVA22007 and vehicle) in the main analysis at Month 6.

Table S 2 Investigational product and comparator: dosage, mode of administration and batch numbers

Investigational product	Dosage form and strength	Manufacturer	Batch nb
NOVA22007 containing CsA	Eye drop emulsion, 1 mg/mL, ocular route	Excel Vision, Annonay, France	W512
Vehicle of NOVA22007	Eye drop emulsion, vehicle, ocular route	Excel Vision, Annonay, France	W725

CsA: ciclosporin; nb: number.

Duration of treatment

Patients were to be randomised to receive one drop once daily of NOVA22007 or vehicle at bedtime, for 6 months. Patients receiving vehicle were to be switched to NOVA22007 after 6 months and for 6 additional months.

Since most of the patients were already receiving lachrymal substitutes prior to enrolment into the study, patients were allowed to use unpreserved AT as frequently as needed throughout the study. AT were provided by the Sponsor during the wash-out.

Statistical methods

The Full Analysis Set (FAS) was used as the primary population for reporting efficacy data; this comprised all patients randomised into the study that received any amount of the study drug and were analysed according to randomised treatment (intention-to-treat principle). The Safety Analysis Set (SAF) was used for reporting safety data; this included all randomised patients for whom there was any evidence they used study medication and for whom any follow-up data were available. Safety analyses were performed using the actual treatment received.

The primary composite responder endpoint was analysed at Month 6 on the FAS using imputed data. A logistic regression model, referred to as the main logistic model, was carried out with 2 factors, “treatment” and “pooled country”. Sensitivity analyses were also performed, using the main logistic model on the Per Protocol Set (PPS), on the FAS using observed data, on the FAS considering the actual treatment received, and use of a Cochran-Mantel-Haenszel (CMH) test controlling for pooled country.

Secondary and other efficacy endpoints were analysed on the FAS and the PPS:

- CFS, OSDI, VAS and CFS-VAS responder rates, and complete corneal clearing rate were analysed using the main logistic model using imputed data.
- Analysis of CFS, OSDI, global VAS, and lissamine green total score change from baseline at each time point (Months 1, 3, and 6) was performed using a repeated measures analysis of variance (ANOVA) with the following fixed factors: “treatment”, “visit”, “pooled country”, and “treatment by visit” interaction. The same model was used to estimate the treatment effect at Month 6, and if significant, the treatment effect at Month 3, and if significant, the treatment effect at Month 1.
- Schirmer test, TBUT, NEI-VFQ-25 and EQ-5D scales, impression cytology (after a logarithmic transformation for HLA-DR [AUF]) and tear film osmolarity were analysed using an analysis of covariance (ANCOVA) model with the following fixed factors: “treatment” and “pooled country”, and the baseline score as covariate. The Shapiro-Wilk test was used to evaluate the normality of the residuals. A supportive analysis was conducted using a CMH test controlling for pooled country.
- The investigator global evaluation of efficacy was analysed using a CMH test controlling for pooled country.

Descriptive statistics for each period and for the difference from baseline were used to analyse the use of AT.

Post hoc analyses were performed:

- with the primary endpoint setting the threshold of improvement of CFS at 3 grades;
- with the CFS responder rate, setting the threshold of improvement of CFS at 3 grades;
- with the primary efficacy endpoint at Months 1, 3 and 6.
- with tear film osmolarity in patients with a score higher than 308 mOsms/L at baseline.

Statistical testing was conducted at a two-tailed significance level of 0.05 for all tests, except for the test on the “treatment by pooled country” interaction effect on the primary efficacy variable ($p<0.1$).

During Part 2, efficacy analyses were descriptive and conducted in the FAS-OPEN. Responder endpoints (CFS-OSDI, CFS, OSDI, global VAS and CFS-VAS responder rates, complete corneal clearing rate) were analysed using frequency distributions and exact 95% confidence intervals (95% CI). Other efficacy endpoints were analysed using means or medians (and standard deviations or range).

Safety and tolerability were to be assessed in terms of treatment-emergent AEs (TEAEs) and ocular TEAEs (post hoc analysis), laboratory data, vital signs, and physical examination. Appropriate summaries of these data were to be presented descriptively by visit and treatment group.

Subject population

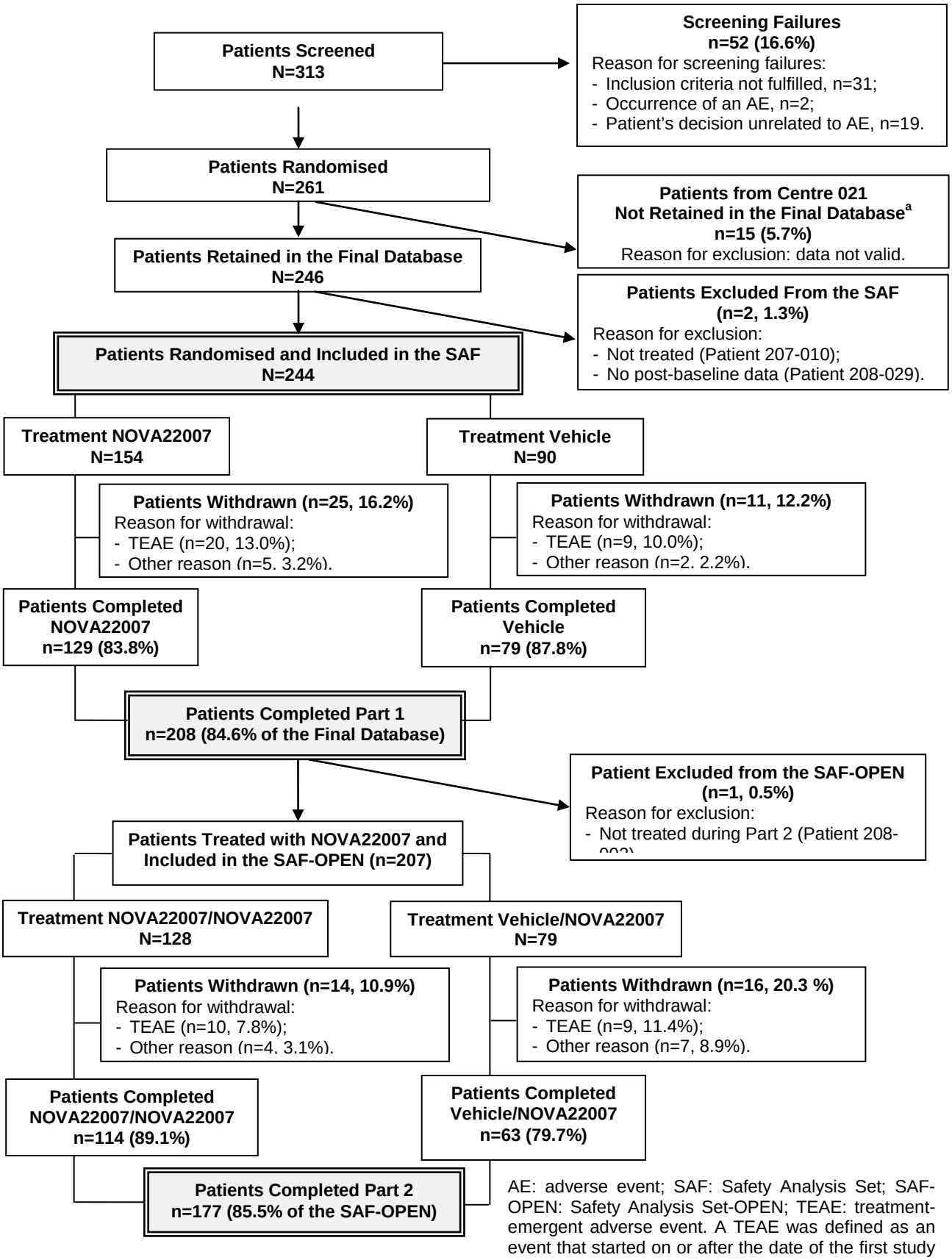
A total of 313 patients were enrolled in this study, of whom 52 failed screening. Overall, 261 patients were randomised, of whom 246 were retained in the final analysis.

Mean age was 61.3 years (range 22.9 to 87.6 years), with 85.3% of the patients being females and 37.6% of the patients having Sjögren’s syndrome. Almost all patients had a diagnosis of DED in both eyes (239/245, 97.6%), and the mean time since diagnosis was 9.1 years (range 0.2 to 31.5 years).

Demographic (age, and gender) and baseline disease characteristics (time since DED diagnosis, Sjögren’s syndrome status, use of lachrymal substitutes) were generally well balanced across the randomised treatment groups.

The rate of discontinuation from study treatment was higher in the active group (16.2% of patients) than in the vehicle group (12.2%). The most common reason for discontinuation from the study was AEs, reported by 13.0% of patients receiving NOVA22007 and by 10.0% of patients who received the vehicle in the first 6 months of the study.

Figure S 1 Flowchart of patient disposition – Part 1 and Part 2



AE: adverse event; SAF: Safety Analysis Set; SAF-OPEN: Safety Analysis Set-OPEN; TEAE: treatment-emergent adverse event. A TEAE was defined as an event that started on or after the date of the first study drug dose.

[a] Reason for non-retention was major breach to good clinical practice (GCP).

Summary of efficacy results

Part 1 (6-month double masked period) – Efficacy Results

Primary endpoint

For the primary responder endpoint of CFS-OSDI at 6 months, NOVA22007 failed to achieve superiority versus vehicle. Based on imputed data and according to treatment as randomised, 44 patients (28.6%) with NOVA22007 and 21 patients (23.1%) with vehicle showed a combined improvement in CFS (by at least 2 grades) and OSDI (by at least 30%) at Month 6 (see Table S 3).

Table S 3 CFS-OSDI Response at Month 6 (FAS)

	NOVA22007	Vehicle	p-value [a]
Imputed data (according to the randomised treatment group)			
N	154	91	p=0.326
Responders, n (%)[a]	44 (28.6)	21 (23.1)	
Non-responders, n (%)	110 (71.4)	70 (76.9)	

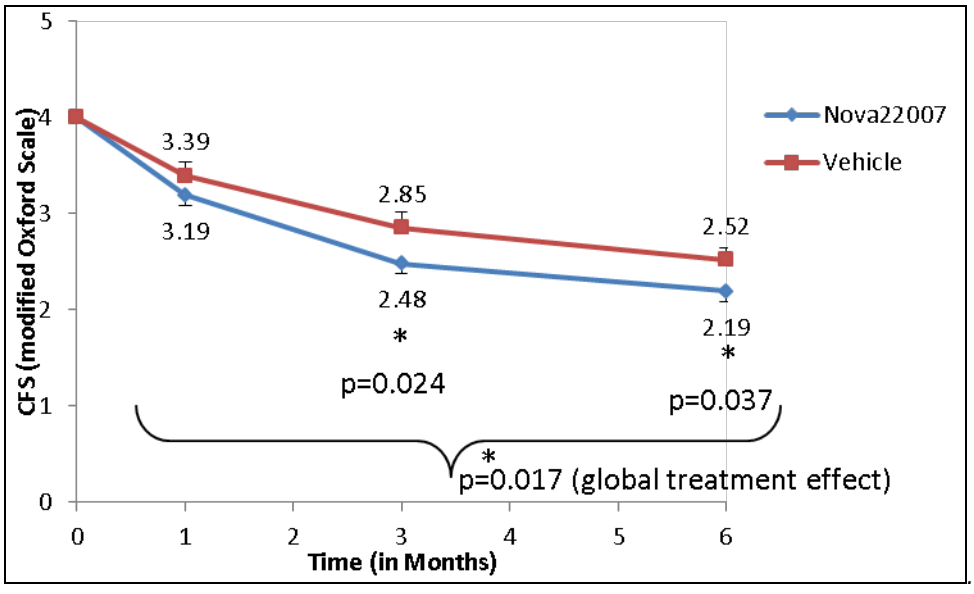
CFS: corneal fluorescein staining; OSDI: ocular surface disease index questionnaire; n: number of patients.
[a] p-value for treatment effect in the logistic regression model.

Sensitivity analyses showed consistent results with the primary analysis.

Secondary Efficacy Endpoints

The CFS score decreased (i.e. improved) over time (p<0.001). Over the 6-month treatment period, a global effect of treatment in favour of NOVA22007 over vehicle was observed (p=0.017) (see Figure S 2 below). The decrease in CFS score from baseline was greater with NOVA22007 than with vehicle at each time point, reaching statistical significance at Month 6 (p=0.037), and as early as Month 3 (p=0.024). At the end of Part 1 (Month 6 Visit), the adjusted mean change in CFS score from baseline was -1.76 with NOVA22007 and -1.42 with vehicle, which was considered clinically significant by the experts.

Figure S 2 Mean CFS Score changes from Baseline to Month 6– Part 1 (FAS)



CFS: corneal fluorescein staining
Sample size at Month 1, 3 and 6: 149, 140 and 132 with NOVA22007, and 88, 89, 83 with vehicle.

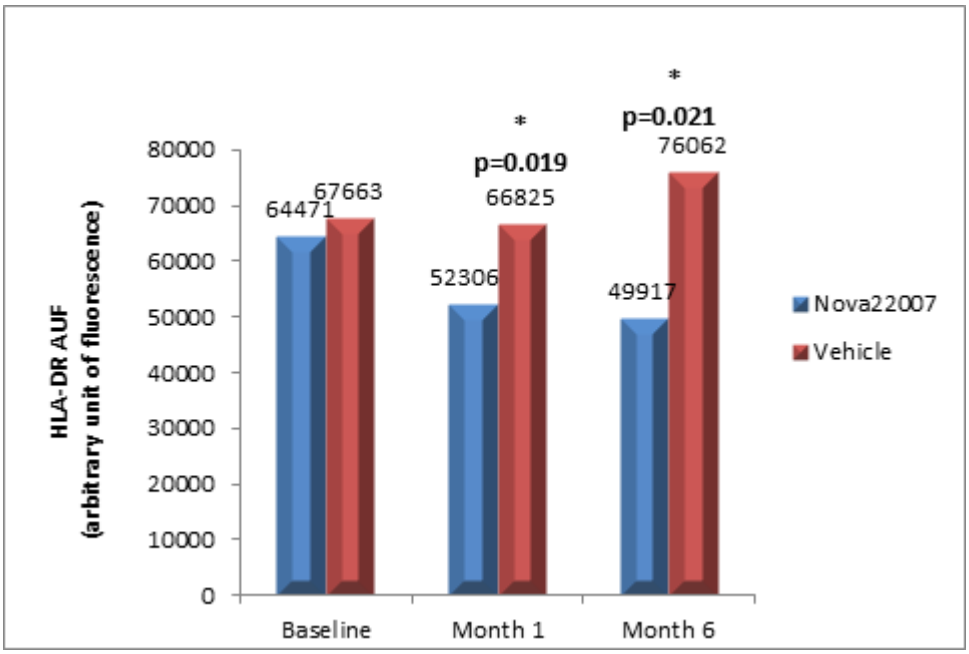
The other responder rates (CFS, OSDI, VAS, CFS-VAS and complete corneal clearing) provided similar results as the primary efficacy endpoint. Complete corneal clearing was achieved within 6 months for 6.5% of patients of NOVA22007 group and for 4.4% of patients of the vehicle group.

Broadly consistent results were seen across the secondary efficacy endpoints, which confirmed a general improvement of the patients in both treatment groups:

- The OSDI score decreased (i.e. improved) over time in the FAS patients (p=0.003). The decrease in OSDI score from baseline was statistically significant in both treatment groups at Months 1, 3 and 6, with no statistically significant difference between treatment groups. After 6 months of treatment, the adjusted mean change in OSDI score from baseline was -13.6 with NOVA22007 and -14.1 with vehicle out of 100 points, which can be considered clinically relevant.
- Similar findings were shown with VAS, Schirmer test, TBUT, lissamine green staining, NEI-VFQ-25, EQ-5D and tear film osmolarity.
- There was a progressive decrease in the use of AT in both treatment groups, with no major differences found between groups however, the number of missing data was high.
- The Investigator rated the patient's improvement as satisfactory or very satisfactory in a slightly higher proportion of patients assigned to NOVA22007 (91 patients, 64.1% vs. 49 patients, 57.0% in the vehicle group); however, the difference between groups was not statistically significant.

Statistically significant difference was observed between treatment groups regarding inflammation as measured by impression cytology (see Figure S 3). The decrease in HLA-DR level of expression (AUF) from baseline was greater with NOVA22007 than with vehicle, with a statistically significant difference at Month 1 (p=0.019) and Month 6 (p=0.021). There was no statistically significant difference between treatments regarding the decrease in the percentage of HLA DR+ cells from baseline to Months 1 and 6.

Figure S 3 Median HLA DR (AUF) from Baseline to Month 6 – Part 1 (FAS)



HLA-DR: human leukocyte antigen-DR.
Sample size at baseline, Month 3 and 6: 119, 76 and 70 with NOVA22007, and 64, 42, 43 in vehicle

The efficacy analyses performed in the PPS supported the findings in the FAS.

Post Hoc Analyses

- A repeated measures analysis of the primary efficacy endpoint conducted in the FAS showed that the CFS-OSDI responder rate increased over time (p<0.0001) and was statistically significantly higher with NOVA22007 than with vehicle (p=0.043).
- When using a more stringent criterion for the patients' improvement (i.e. improvement in CFS score of at least 3 grades instead of 2), the CFS-OSDI responder rate was statistically significantly higher (p=0.016) with NOVA22007 (29 patients, 18.8% vs. 7 patients, 7.7% with vehicle). The chance to be a responder was approximately 3 times higher with NOVA22007 than with vehicle (odds ratio: 2.9, 95% CI [1.3;7.7]).
- Similarly, the chance to improve CFS by at least 3 grades within 6 months of treatment was approximately 3 times higher with NOVA22007 than with vehicle (odds ratio: 3.0, 95% CI [1.5;6.3]).
- Following experts' recommendation, tear film osmolarity was analysed in patients with osmolarity level >308 mOsms/L at baseline, a threshold known to be indicative of DED. The analysis, which was performed in 55 patients, showed a statistically significantly greater improvement in the worst tear film osmolarity from baseline to Month 6 with NOVA22007 than with vehicle (p=0.048).

Part 2 (6-month open label extension period) – Efficacy Results

Among the 208 patients who completed Part 1, 207 entered Part 2 and all received NOVA22007, allowing a descriptive analysis of the long-term efficacy of NOVA22007 over 12 months. Globally, the improvement achieved during the first 6 months in both treatment groups was maintained during the last 6 months of the study.

The CFS-OSDI responder rate continued to increase during the last 6 months of the study in both groups to reach 39.1% at Month 12 in the NOVA22007/NOVA22007 group (patients

who received NOVA22007 for 12 months) and 38.0% in the vehicle/NOVA22007 group (patients who received the vehicle for 6 month and were then switched to NOVA22007). The vehicle/NOVA22007 group caught up with the NOVA22007/NOVA22007 group while being under NOVA22007 treatment.

The other responder rates (CFS, OSDI, VAS and CFS-VAS) increased between Month 6 and Month 12, with no marked differences between groups except the CFS responder rate which was higher in the NOVA22007/NOVA22007 group (65.6% vs. 54.4% in the vehicle/NOVA22007 group) at Month 12. Catching up in the vehicle/NOVA22007 group during the last 6 months was also observed for complete corneal clearing (11.4% at Month 12, versus 12.5% in the NOVA22007/NOVA22007 group), the Investigator's global evaluation of efficacy at Month 12 (71.7% of patients showing a satisfactory/very satisfactory improvement in the NOVA22007/NOVA22007 group vs. 69.9%), and HLA-DR expression. During the last 6 months of the study, median HLA-DR level of expression (AUF) decreased in the vehicle/NOVA22007 group (-5065.5 AUF), whereas it did not change in the NOVA22007/NOVA22007 group (+314.0 AUF). Other variables (Schirmer test, TBUT and NEI-VFQ-25 and EQ-5D) remained relatively stable in both treatment groups. In addition, the percentage of HLA-DR+ cells varied over time but did no markedly differ between baseline and Month 12 in both groups. The analysis of the use of AT and tear film osmolarity was hampered by the low sample size for both variables.

Summary of safety results

Two hundred and eight patients (208) completed Part 1 (6-month double masked period) of which 129 patients were exposed to NOVA22007 for 6 months. One hundred and seventy-seven patients (177) completed Part 2, of which 114 patients received NOVA22007 for 12 months and 63 patients received NOVA22007 for 6 months during Part 2.

Part 1 (6 month double masked period) – Safety Results

Overall, during Part 1 of the study, 88 patients (57.1%) treated with NOVA22007 reported 175 TEAEs and 42 patients (46.7%) treated with vehicle reported 88 TEAEs (see Table S 4).

Table S 4 Adverse events in any category, from randomisation to Month 6

TEAEs during Part 1 (SAF)	NOVA22007 N=154		Vehicle N=90	
	n (%)	n events	n (%)	n events
Any TEAE	88 (57.1)	175	42 (46.7)	88
Any treatment-related TEAE	57 (37.0)	95	19 (21.1)	30
Any ocular TEAE	66 (42.9)	112	27 (30.0)	44
Any treatment-related ocular TEAEs	57 (37.0)	90	18 (20.0)	29
Any TEAE leading to discontinuation [a]	21 (13.6)	34	9 (10.0)	11
Any ocular TEAE leading to discontinuation	18 (11.7)	29	6 (6.7)	8
Any severe ocular TEAE	9 (5.8)	16	5 (5.6)	8
Any SAE [b]	6 (3.9)[b]	6[b]	6 (6.7)	6
Any treatment-related SAEs	0 (0.0)	0	1 (1.1)	1
Any ocular SAE	0 (0.0)	0	1 (1.1)	1
Deaths	0 (0.0)	0	0 (0.0)	0

TEAE: treatment-emergent adverse event; SAF: Safety Analysis Set; SAE: serious adverse event; n patients: number of patients; n events: number of events.
If a patient had multiple occurrences of an event, the patient was counted only once in the corresponding patient count.
[a] *This category is about TEAEs that led to permanent discontinuation of treatment. All patients who stopped treatment were also discontinued from the study, except Patient 208-002 who continued the study and completed Part 1*
[b] *There was 1 SAE (staphylococcal infection) that started during Part 1, but its seriousness (i.e. event requiring hospitalization) was known by the Investigators after Part 1 database lock.*

TEAEs considered by the Investigator to be treatment-related were reported in a higher proportion of patients treated with NOVA22007 (57 patients, 37.0%) than with vehicle (19 patients, 21.1%). In both treatment groups, all treatment-related TEAEs were ocular TEAEs, except the following events: headache (3 patients, 1.9%, treated with NOVA22007), tachycardia (2 patients, 1.3%, treated with NOVA22007) and skin irritation (1 patient, 1.1%, treated with vehicle). Ocular TEAEs were considered by the Investigator to be treatment-related in a higher proportion of patients treated with NOVA22007 (90 events in 57 patients, 37.0%) than with vehicle (29 events in 18 patients, 20.0%). In each treatment group, the most frequently reported ocular TEAE was instillation site pain, which was reported in a higher proportion of patients treated with NOVA22007 (47 patients, 30.5%) than with vehicle (8 patients, 8.9%). In almost all cases, instillation site pain was considered by the Investigator to be related to treatment (45 patients, 29.2%, in the NOVA22007 group and 8 patients, 8.9%, in the vehicle group). Apart from the instillation site pain, the ocular TEAEs reported in at least 2.5% of patients in the NOVA22007 group were blepharitis (6 patients, 3.9%), and eye irritation and ocular hyperemia (each in 4 patients, 2.6%); and in the vehicle group, eye pain and eye pruritus (each in 4 patients, 4.4%), and photophobia and reduced visual acuity (each in 3 patients, 3.3%). Apart from the instillation site pain, the treatment-related ocular TEAEs reported in at least 1.5% of patients in the NOVA22007 group were eyelid edema and instillation site erythema (each in 3 patients, 1.9%); and in the vehicle group, photophobia (in 3 patients, 3.3%), and eye irritation and reduced visual acuity (each in 2 patients, 2.2%). Considering all ocular TEAEs except instillation site pain, there were no clear trends for an increased incidence of any ocular TEAE (related or not) with either treatment.

Most non-ocular TEAEs were of mild or moderate severity and there were no trends for an increased incidence of these events (related or not) with either treatment. Most ocular TEAEs were of mild or moderate severity. Severe ocular TEAEs, which were all treatment-related, were reported in a higher proportion of patients treated with NOVA22007 (16 events in 9 patients, 5.8%) than with vehicle (8 events in 5 patients, 5.6%)

Treatment was discontinued due to TEAEs in 21 patients (13.6%) treated with NOVA22007 and 9 patients (10.0%) treated with vehicle. Ocular TEAEs led to permanent discontinuation of treatment in a higher proportion of patients treated with NOVA22007 (29 events in 18 patients, 11.7%) than with vehicle (8 events in 6 patients, 6.7%).

A total of 12 SAEs were reported during Part 1, with only 1 event being related to treatment (a severely reduced visual acuity in 1 patient treated with vehicle). Treatment-emergent SAEs were reported in a similar proportion of patients treated with NOVA22007 (6 patients, 3.9%, who reported 6 SAEs) and vehicle (6 patients, 6.7%, who reported 6 SAEs). There were no AESIs and no deaths during Part 1.

There were no remarkable changes in BCDVA, IOP, or in vital signs. Treatment with NOVA22007 tended to improve moderate to very severe signs of tear film debris to a greater extent than treatment with vehicle. In contrast, treatment with vehicle tended to improve severe lid erythema, moderate signs of Meibomian glands plugging and moderate conjunctival edema. There were no other differences between treatments at slit lamp examination. Very severe ocular signs reported at baseline (lid erythema, conjunctival edema or tear film debris) had disappeared by Month 6 in both treatment groups, except for one case of very severe tear film debris in the vehicle group.

Four patients had measurable CsA level less than the upper limit of quantification (ULOQ) of 5 ng/mL, which is considered negligible. High CsA levels were found in 3 patients treated with NOVA22007 (1.9%) but these patients were already receiving systemic CsA (Sandimmun), which was allowed during the study as per the study protocol, provided treatment remained stable throughout the course of the study.

Part 2 – Safety Results

A total of 54 patients (42.2%) in the NOVA22007/NOVA22007 group reported 95 TEAEs and 28 patients (35.4%) in the vehicle/NOVA22007 group reported 49 TEAEs (see Table S 5).

Treatment-related TEAEs were reported in a higher proportion of patients in the vehicle/NOVA22007 group (26 events in 18 patients, 22.8%) than in the NOVA22007/NOVA22007 (32 events in 19 patients, 14.8%). In the vehicle/NOVA22007 group, all treatment-related TEAEs were ocular TEAEs. In the NOVA22007/NOVA22007 group, all treatment-related TEAEs were ocular TEAEs, except the following events: stomatitis (1 patient, 0.8%), fatigue (1 patient, 0.8%), headache (1 patient, 0.8%) and increased upper airway secretion (1 patient, 0.8%). Ocular TEAEs were considered by the Investigator to be treatment-related in a higher proportion of patients in the vehicle/NOVA22007 group (26 events in 18 patients, 22.8%) than in the NOVA22007/NOVA22007 (28 events in 19 patients, 14.8%).

Table S 5 Adverse events in any category, from Month 6 to Month 12

TEAEs during Part 2 (SAF-OPEN)	NOVA22007 N=128		Vehicle N=79	
	n (%)	n events	n (%)	n events
Any TEAE	54 (42.2)	95	28 (35.4)	49
Any treatment-related TEAE	19 (14.8)	32	18 (22.8)	26
Any ocular TEAE	34 (26.6)	48	23 (29.1)	34
Any treatment-related ocular TEAEs	19 (14.8)	28	18 (22.8)	26
Any TEAE leading to discontinuation [a,b]	10 (7.8)[b]	17[b]	9 (11.4)	9
Any ocular TEAE leading to discontinuation [b]	9 (7.0)[b]	11[b]	7 (8.9)	7
Any severe ocular TEAE	1 (0.8)	2	1 (1.3)	1
Any SAE	8 (6.3)	8	2 (2.5)	2
Any treatment-related SAEs	0 (0.0)	0	0 (0.0)	0
Any ocular SAE	0 (0.0)	0	0 (0.0)	0
Deaths	0 (0.0)	0	0 (0.0)	0

TEAE: treatment-emergent adverse event; SAF-OPEN: Safety Analysis Set-OPEN; SAE: serious adverse event; n patients: number of patients; n events: number of events.
If a patient had multiple occurrences of an event, the patient was counted only once in the corresponding patient count.
[a] This category is about TEAEs that led to permanent discontinuation of treatment. All patients who stopped treatment were also discontinued from the study.
[b] This category includes TEAEs that started during Part 2 and led to permanent discontinuation during Part 2, but also 4 TEAEs, which started during Part 1 and led to permanent discontinuation during Part 2. These TEAEs were instillation site pain (Patients 006-004, 014-002 and 025-002) and staphylococcal infection (Patient 313-014), all reported in the NOVA22007/NOVA22007 group.

In each treatment group, the most frequently reported ocular TEAE was instillation site pain, which was reported in a higher proportion of patients in the vehicle/NOVA22007 (15 patients, 19.0%) than in the NOVA22007/NOVA22007 group (10 patients, 7.8%). All reports of instillation site pain were considered by the Investigator to be related to treatment. Apart from the instillation site pain, the ocular TEAEs reported in at least 2% of patients in the NOVA22007/NOVA22007 group were keratitis (3 patients, 2.3%); and in the vehicle/NOVA22007 group, eye irritation (3 patients, 3.8%), and keratitis (2 patients, 2.5%). Apart from the instillation site pain, the treatment-related ocular TEAEs reported in at least 1.5% of patients in the NOVA22007/NOVA22007 group were eye irritation, eye pruritus and ocular hyperemia (each in 2 patients, 1.6%); and in the vehicle/NOVA22007 group, eye irritation (in 3 patients, 3.8%). Considering all ocular TEAEs except instillation site pain, there were no clear trends for an increased incidence of any ocular TEAE (related or not) in either group.

Most non-ocular TEAEs were of mild or moderate severity and there were no trends for an increased incidence of the events (related or not). Most ocular TEAEs were of mild or moderate severity. Severe ocular TEAEs, which were all considered to be related to treatment, were reported in a similar proportion of patients in the NOVA22007/NOVA22007 group (2 events in 1 patient, 0.8%) and in the vehicle/NOVA22007 group (1 event in 1 patient, 1.3%).

The proportion of patients who were discontinued after the Month 6 Visit due to a treatment-related TEAE was slightly higher in the NOVA22007/NOVA22007 group (10 patients, 7.8%) than in the vehicle/NOVA22007 group (9 patients, 114%). Ocular TEAEs led to permanent discontinuation of treatment in a similar proportion of patients in the NOVA22007/NOVA22007 group (11 events in 9 patients, 7.0%) and in the vehicle/NOVA22007 group (7 events in 7 patients, 8.9%).

A total of 10 SAEs were reported during Part 2. Treatment-emergent SAEs were reported in a higher proportion of patients in the NOVA22007/NOVA22007 group (8 patients, 6.3%, who reported 8 SAEs) than in the vehicle/NOVA22007 group (2 patients, 2.5%, who reported 2 SAEs). Among these 10 SAEs, none were considered to be related to treatment. There were no AESIs and no deaths during Part 2.

There were no remarkable changes in BCDVA, IOP, or in vital signs. At Slit Lamp Examination, most patients had no or mild ocular signs during the last 6 months of the study. Severe ocular signs were reported in both groups during the Month 6-Month 12 period for lid erythema, conjunctival erythema and tear film debris. At Month 12, severe ocular signs were still reported in the NOVA22007/NOVA22007 group for lid erythema (n=1, 0.9%) and conjunctival erythema (n=2, 1.7%) and in the vehicle/NOVA22007 group for lid erythema (n=1, 1.5%), conjunctival erythema (n=1, 1.5%) and tear film debris (n=1, 1.5%). Only 1 patient (patient 001-006) in the vehicle/NOVA22007 group reported very severe signs of tear film debris at Months 6, 9 and 12.

At Month 12, the systemic CsA exposure profile appeared consistent with the profile observed until Month 6, whether the patient received NOVA22007 for 12 months or whether the patient was switched to NOVA22007 after 6 months on vehicle.

Overall safety (12 months)

Safety analyses over 12 months were performed in the 154 patients who received NOVA22007 during Part 1 of the study. Of the 128 patients who joined Part 2 and received NOVA22007 during Part 1, 114 completed Part 2, and were thus exposed to NOVA22007 for 12 months. Throughout the 12-month study, 113 out of 154 patients (73.4%) reported 275 TEAEs (see Table S 6).

Approximately half these events (128 events) were considered by the Investigator to be treatment-related. They were reported in 70 patients (45.5%). A total of 86 patients (55.8%) reported 160 ocular TEAEs, 118 of which were considered by the Investigator to be treatment-related. The majority of the ocular TEAEs occurred during the first 6 months of treatment with NOVA22007 (112 events, versus only 48 events during the last 6 months). All the TEAEs related to the treatment with NOVA22007 were ocular TEAEs, except the following events: headache (4 patients, 2.6%), tachycardia (2 patients, 1.3%), stomatitis, fatigue and increased upper airway secretion (each in 1 patient, 0.6%).

The most frequently reported treatment-related ocular TEAE was instillation site pain. Over 12 months, approximately one third of the patients who received NOVA22007 (54 patients, 35.1%) experienced instillation site pain. The other most frequently reported treatment-related ocular TEAEs were eye irritation, eyelid edema, ocular hyperemia, instillation site erythema (each in 4 patients, 2.6%), and dry eye, eye pruritus and instillation site lacrimation (each in 3 patients, 1.9%). All the other treatment-related ocular TEAEs were reported in less than 1.5% of the patients.

Table S 6 Adverse events in any category, from randomisation to Month 12

TEAEs during Part 1 and Part 2 (SAF Patients Who Received NOVA22007 during Part 1)	NOVA22007 (SAF Patients) N=154	
	n (%) patients	n events
Any TEAE	113 (73.4)	275
Any treatment-related TEAE	70 (45.5)	128
Any ocular TEAE	86 (55.8)	160
Any treatment-related ocular TEAEs	70 (45.5)	118
Any TEAE leading to discontinuation [a]	31 (20.1)	51
Any ocular TEAE leading to discontinuation [b]	27 (17.5)	40
Any severe ocular TEAE	11 (7.1)	19
Any SAE	14 (9.1)	14
Any treatment-related SAEs	0 (0.0)	0
Any ocular SAE	0 (0.0)	0
Deaths	0 (0.0)	0

TEAE: treatment-emergent adverse event; SAE: serious adverse event; n patients: number of patients; n events: number of events; SAF: Safety Analysis Set.
If a patient had multiple occurrences of an event, the patient was counted only once in the corresponding patient count.
[a] *This category is about TEAEs that led to permanent discontinuation of treatment. All patients who stopped treatment were also discontinued from the study.*

Most TEAEs were of mild or moderate severity, regardless of their relationship to treatment. Among the 275 events that were reported over 12 months in patients treated with NOVA22007, 25 events were reported as severe in 16 patients (10.4%). The most frequently reported severe ocular TEAEs (all related to treatment) were installation site pain (8 patients, 5.2%), eyelid edema and instillation site erythema (each in 2 patients, 1.3%), blepharitis, chalazion, dry eye, eyelid pruritus, ocular hyperemia, instillation site irritation (each in 1 patient, 0.6%).

Over 12 months, treatment with NOVA22007 was discontinued due to TEAEs in 31 patients in total (20.1%). Approximately two thirds of the permanent discontinuations occurred during the first 6 months (21 patients, 13.6%) and one third occurred during the last 6 months (10 patients, 6.5%).

A total of 14 SAEs were reported over 12 months, none of which were considered related to the treatment with NOVA22007. There were no ocular SAEs over the 12-month study. The other safety analyses performed over 12 months did not raise any specific safety concerns.

Conclusions

- Overall, the baseline characteristics of the patient population were consistent with the intended study population and there were no notable imbalances between treatment groups.

- The treatment with NOVA22007 1 mg/mL for 6 months was associated with an improvement in both subjective symptoms and objective signs of DED in patients with or without Sjögren's syndrome, as shown in a previous Phase III study (Siccanove Study – NGV06C103). However, NOVA22007 1 mg/mL did not perform better than vehicle when considering the CFS-OSDI responder rate used as the primary endpoint at 6 months.

- Despite the lack of difference between treatment groups in the primary efficacy endpoint at Month 6, NOVA22007 1 mg/mL provided a greater improvement in corneal staining over time, and the benefit over vehicle was significant as early as Month 3.

- Although it is acknowledged that no difference in effect on symptoms was seen in NOVA22007- *vs*. vehicle-treated patients, symptoms did markedly improve in both groups over time. Both NOVA22007 and the vehicle were similarly efficacious on symptom improvement. The OSDI improvement in both groups after 6 months was 14 points on average, which can be considered clinically relevant since above the MCID as described by Miller and colleagues in 2010.

- None of the other secondary efficacy endpoints revealed any differences between treatments; however, treatment with NOVA22007 reduced HLA-DR expression, whereas the vehicle had almost no effect on this parameter measuring ocular surface inflammation over a 6-month period, suggesting that the study drug reduced the conjunctival inflammation.

- Further improvement, although of smaller magnitude, was achieved by extending treatment with NOVA22007 1 mg/mL for 6 additional months. The responder rate of complete corneal clearing, which was low at Month 6 in both treatment groups, almost doubled when all patients received NOVA22007 1 mg/mL.

- The safety and tolerability of NOVA22007 given once daily in this study for 12 months did not reveal any systemic findings that could have been foreseen due to the nature of the compound.

- Apart from the instillation site pain, which was reported in a higher proportion of patients treated with NOVA22007 1 mg/mL than with vehicle, there were no clear trends for an increased incidence of any ocular TEAE with either treatment. During the first 6 months of the study, permanent discontinuation due to an ocular event (mainly instillation site pain) was more frequently observed in patients treated with NOVA22007 1 mg/mL than patients treated with vehicle. These results were corroborated by the safety analyses performed over 12 months, which show that approximately one third of the patients who received NOVA22007 experienced instillation site pain.

- Most of the ocular TEAEs reported in patients treated with NOVA22007 1 mg/mL occurred during the first 6 months of treatment. Over 12 months, most of them were of mild or moderate severity and there were no SAEs related to treatment with NOVA22007 1 mg/mL.

- Overall, the present study confirms the positive benefit-to-risk ratio of NOVA22007 1 mg/mL in patients with severe DED, as previously shown in the Siccanove 6-month Study.

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