Title of Study:	A Phase III, Multicentre, Randomized, Controlled, Double-Masked Trial of NOVA22007 (Ciclosporin 0.1%) Ophthalmic Cationic Emulsion versus Vehicle in Patients with Moderate to Severe Dry Eye Syndrome.
Coordinating Investigator:	Professor Christophe Baudouin
Study centres:	61 centres in six European countries: 13 centres in France; 13 centres in Germany; 11 centres in Italy; 10 centres in the Czech Republic; 9 centres in Spain; 5 centres in the United Kingdom (UK).
Publication:	Not applicable
Phase of development:	Phase III
Study period:	
First Patient First Visit	27 Sep 2007
Last Patient Last Visit	08 Sep 2009
Objectives:	
Primary:	To demonstrate the superiority of NOVA22007 (Ciclosporin 0.1%) ophthalmic cationic emulsion versus Vehicle administered once daily in patients with moderate to severe dry eye syndrome after a 6-month treatment period.
Secondary:	To compare the ocular tolerance and systemic safety of NOVA22007 ophthalmic cationic emulsion versus Vehicle administered once daily in patients with moderate to severe dry eye syndrome, after a 6-month treatment period.
Methods:	This was a Phase III, multicenter, randomized, double-masked, parallel group, controlled trial designed to evaluate the safety and efficacy of NOVA22007 ophthalmic cationic emulsion in comparison to negative control (Vehicle) administered once daily in patients with moderate to severe dry eye syndrome. The study was designed as a superiority trial. At Screening, patients discontinued use of any topical ophthalmic treatments related or not related to dry eye (including their own artificial tears), if any, and entered a 2-week wash-out phase during which they used a regimen of unpreserved artificial tears (provided by the Sponsor) as recommended by the Investigator, but no more than one drop eight times daily in each eye. Patients were instructed in the optimal technique for ophthalmic drop instillation with artificial tears.

	At the completion of the 2-week wash-out period (Baseline/Day 0), patients who met the eligibility criteria were randomly assigned (1:1) to one of the two treatment arms: • NOVA22007 • Vehicle (negative control – NOVA22007 0%) Randomization was centralized and stratified by Sjögren syndrome (presence vs. absence). During the treatment phase, patients were instructed to instil one drop of study medication once daily in both eyes at bedtime for 6 months. Patients were allowed to use unpreserved artificial tears (only those provided by the Sponsor) as needed, but not more than one drop, six times daily, in each eye, during the entire study period (from Day 0). Patients were instructed not to use the artificial tears within 30 minutes before or after use of the study medication. Patients were followed for a 6-month period, with evaluations occurring at scheduled intervals (Days 28, 84, and 168). Patients exited the study at the 6-month follow-up visit.
Number of patients: **Planned:**	482 patients were to be randomized into the study (241 in each treatment group) in order to obtain approximately 410 evaluable patients (205 in each treatment group) at the end of the study (taking into account a 15% drop-out/discontinuation rate).
Analysed:	Safety population: N = 492 Full Analysis Set (FAS) population: N = 489 Per-Protocol (PP) population: N = 347
Diagnosis and main criteria for inclusion:	Males or female patients, aged ≥18 years, who had moderate to severe dry eye condition at Baseline persisting despite conventional management (which could include artificial tear drops, gels or ointments and punctual occlusion), and defined as the following: • At least one moderate to severe symptom of dry eye with a score ≥2 (severity graded on a 4-point scale) i.e., burning/stinging, foreign body sensation, itching, eye dryness, pain, blurred vision or sticky feeling and photophobia, **and,** • Tear break-up time (BUT) ≤8 seconds, **and,**

	• Corneal fluorescein staining ≥2 and ≤4 (modified Oxford scale, scale 0-5), **and,** • Schirmer tear test without anaesthesia of ≥2 mm/5 min and <10 mm/5 min, **and,** • Lissamine green staining >4 (Van Bijsterveld scale, scale 0-9). The same eye (eligible eye) was to fulfil all the above criteria. Eligible patients were to provide written informed consent and be willing and able to undergo and return for scheduled study-related examinations. Exclusion criteria can be found in Section 9.3.2 of this Clinical Study Report (CSR).
Investigational medicinal product:	NOVA22007 is a sterile, ophthalmic cationic emulsion containing 0.1% CsA. NOVA22007 emulsion was made of two parts: an oily phase and an aqueous phase.
Dose and mode of administration, batch numbers:	Bilateral instillation of one drop of study medication (NOVA22007 0.1% eye drops or NOVA22007 0% [Vehicle] eye drops) into the lower conjunctival sac, once daily at bedtime for 6 months. During the study visit, the instillation was conducted at the site (Day 0, Month 1, Month 3 and Month 6 visits). Each single-unit container was to be used only once (for instillation in both eyes). Changes in the treatment regimen during the study were not permitted. Two batches of study medication were used during the study: Manufacturer: Holopack — Manufacturer: Excelvision Date: 21-25 Sep 2006 — Date: 27 Aug 2008 Batch Number: Z06E49 — Batch number: S137
Duration of treatment:	This study consisted of three phases: screening, a 2-week wash-out period (between Screening and Baseline visits), and a 6-month double-masked treatment phase (Baseline to Month 6 visits). There were five scheduled visits: • Screening Visit (Day -14) • Baseline Visit (Day 0) • Month 1 (Day 28 ± 3 days) • Month 3 (Day 84 ± 7 days) • Month 6 – Final Visit (Day 168 ± 14 days)

Vehicle (negative control):	NOVA22007 0% (Vehicle) is sterile, drug-free, cationic ophthalmic emulsion containing 0% CsA and made of two parts: an oily phase and an aqueous phase.
Dose and mode of administration, Batch numbers:	Administration of the Vehicle was identical to the active medication. Two batches of Vehicle were used during the study: Manufacturer: Holopack — Manufacturer: Excelvision Date: 14 & 15 Sep 2006 — Date: 01 Sep 2008 Batch Number: Z01E47 — Batch number: S293
Criteria for evaluation:	
Efficacy:	Primary endpoints: Objective parameter: • Change in corneal fluorescein staining (modified Oxford scale) from Baseline to Day 168. Subjective parameter: • Change in global score of ocular discomfort unrelated to study medication instillation (VAS), from Baseline to Day 168. Secondary endpoints: • Change in corneal fluorescein staining (modified Oxford scale) from Baseline to Days 28 and 84. • Change in Lissamine green staining of the interpalpebral conjunctiva (Van Bijsterveld scale) from Baseline at Days 28, 84, 168. • Change in Schirmer's tear test performed from Baseline at Days 84, 168. • Change in each symptom of ocular discomfort unrelated to study medication instillation from Baseline to Days 168 (VAS scale). • Comparison of percentage of responders based on improvement in ocular symptoms unrelated to study medication instillation assessed on VAS, between the two treatment groups from Baseline to Days 168. • Change in tear break-up time (BUT) from Baseline at Days 28, 84, 168. • Change in Ocular Surface Disease Index© (OSDI©) questionnaire from Baseline to Days 28, 84 and 168. • Comparison of percentage of complete responders, i.e. complete clearance of corneal fluorescein staining between the two treatments groups, from Baseline to Day 168. • Global evaluation of efficacy by the Investigator at

	Days 28, 84, 168. • Average number of times per day artificial tears were used the week preceding the visits on Days 28, 84 and 168. • Number of days artificial tears were not used during the week preceding the visits on Days 28, 84 and 168.
Local Ocular Tolerance:	The endpoints relating to local ocular tolerance were: • Each symptom of ocular discomfort (related to instillation of the study medication) on Days 0, 28, 84 and 168 (15 minutes after instillation and between the study visits) using a 3-point severity scale. • Slit lamp examination performed in each eye at Screening and on Days 0, 28, 84 and 168.
Safety:	The safety endpoints of this study were: • Best corrected distance visual acuity (BCDVA) measured in each eye on Days 0, 84 and 168. • Intraocular pressure (IOP) measured in each eye on Days 0, 84 and 168. • Ocular and systemic AEs. • Vital signs (sitting blood pressure, heart rate and respiratory rate) at Days 0 and 168. • CsA blood levels at Day 0 and 168 (subset of 140 patients in selected sites). • Impression cytology at Day 0 and 168 (subset of 70 patients in selected sites).
Statistical Methods:	The statistical analyses of tolerance and safety were performed on the basis of the Safety population. The analyses of baseline information and efficacy data were performed for both the Full Analysis Set (FAS) population and the Per Protocol (PP) population. Descriptive statistics were used for quantitative variables, and frequencies and percentages for categorical variables, stratifying by treatment group. For the efficacy variables recorded for both eyes, descriptive statistics and statistical analyses were only performed for the worst eye. The 'worst' eye (defined as the eligible eye with the highest modified Oxford score for corneal staining at Baseline) was used for the determination of efficacy. If both eyes had the same score at Baseline, the right eye was to be considered. Safety variables recorded in both eyes were summarized for both the worst eye and other eye separately. Statistical hypothesis testing was performed using an analysis

	of covariance (ANCOVA) model. Several additional analyses were performed on the co-primary endpoints to show robustness of the primary results. These included using the PP population, the addition of terms for country, and the treatment by country interaction to the statistical model, and the main model fitted to observed data only. Secondary analyses were performed at Month 1 (Day 28) and Month 3 (Day 84) in order to detect a potential early effect of the treatment. Analyses of key efficacy variables were also stratified by Sjögren/non-Sjögren patients. Some secondary endpoints were analysed using a repeated measures ANCOVA.

SUMMARY – CONCLUSIONS

Four hundred and ninety-six (496) patients were enrolled, with 242 patients receiving NOVA22007 and 250 patients received the Vehicle treatment. Four patients were randomized but not treated. The majority of patients completed the study (83.5%).

The Full Analysis Set (N=489) included mostly Caucasian (98.8%) and female (84.5%) patients. Mean age overall was 58.2 years. The majority of female patients were post-menopausal (71.2%).

Overall, 177/489 patients (36.2%), 89 in the NOVA22007 group and 88 in the Vehicle group had Sjögren's syndrome, by which the treatment groups were stratified. The treatment groups were comparable in terms of demographics and baseline characteristics. The PP population included 347 patients.

EFFICACY RESULTS:

Primary Efficacy Endpoint

The co-primary endpoints of this study were the change in corneal fluorescein staining (modified Oxford scale) from Baseline to Day 168 and the change in global score of ocular discomfort unrelated to study medication instillation from Baseline to Day 168.

For the Full Analysis Set, the mean change in corneal fluorescein staining from Baseline to Day 168 was -1.05 (NOVA22007 and -0.82 (Vehicle). A statistically significant treatment effect in favour of NOVA22007 was shown using an ANCOVA model (p=0.009). The improvement in this objective endpoint indicates a therapeutic benefit in comparison to Vehicle treatment. These findings were supported by a non-parametric analysis as well as in the PP population and in all the predefined robustness analyses.

For the Full Analysis Set, the mean change in global ocular discomfort score from Baseline to Day 168 was -12.82 (NOVA22007) and -11.21 (Vehicle) showing a noticeable improvement in both groups. The difference between treatment groups was not statistically significant using an ANCOVA model (p=0.808) for this subjective

endpoint. Similar results were observed in the PP population.

Secondary Efficacy Endpoint

For the Full Analysis Set, the mean change in corneal fluorescein staining score from Baseline to Day 28 was -0.77 and -0.52 for the NOVA22007 and Vehicle groups, respectively. At Day 84, the mean change from Baseline was -0.92 and -0.70 for the NOVA22007 and Vehicle groups, respectively. A statistically significant treatment effect in favour of NOVA22007 was shown at Day 28 (p=0.002) and Day 84 (p=0.030), which indicates that the improvement in the objective sign is present as early as Month 1 of treatment.

The change in lissamine green staining of the interpalpebral conjunctiva from Baseline to Day 28 (-1.52 vs. -1.30), Day 84 (-2.12 vs. -1.74) and Day 168 (-2.37 vs. -2.18) were slightly greater for the NOVA22007 group. A statistically significant treatment effect in favour of NOVA22007 was shown for the global effect of treatment, following a repeated measures ANCOVA (p=0.048). These results support the results of the co-primary endpoint (change in corneal fluorescein staining).

The percentage of responders on ocular discomfort (VAS) (defined as a decrease of at least 25%) was 40.66% for the NOVA22007 group vs. 39.11% for the Vehicle group at Day 28, 48.13% vs. 45.97% at Day 84, and 50.21% vs. 41.94% at Day 168. The difference in favour of NOVA22007 at Day 168 was statistically significant (p=0.048).

Individually, ocular discomfort symptoms unrelated to study medication scores were not statistically significantly different between treatment groups, with the exception of burning/stinging score (p=0.038 in favour of the Vehicle group). The PP population supported the results of the Full Analysis Set.

At Baseline and all the follow-up visits the use of artificial tears during the study was comparable between treatment groups. There were also no between-group differences in Schirmer's test, tear break-up time, complete responders (corneal fluorescein staining score of zero on the modified Oxford scale), OSDI score and global evaluation of efficacy by the Investigator.

Post-hoc analyses:

Post-hoc analyses were performed on a subset of more severely affected patients, i.e., with corneal fluorescein staining score ≥ 3 and OSDI score ≥ 23 at baseline. In this subset of 128 patients in the NOVA22007 group and 118 in the Vehicle group, statistically significant between-group differences in favour of NOVA22007 were observed for the percentage of responders on corneal fluorescein staining and the percentage of responders on both a sign (improvement in CFS) and a symptom (improvement in OSDI score), i.e., in the same patient. Specifically, the outcomes were as follows:

- The percentage of responders on a sign, defined as patients with at least 2 grades improvement in corneal fluorescein staining on the modified Oxford scale was 32.03% vs. 20.34% at Day 168 for the NOVA22007 and Vehicle groups respectively (p=0.047).
- The percentage of responders for a symptom defined as patients with at least 30%

improvement in OSDI was 42.19% vs. 33.05% at Day 168 for the NOVA22007 and Vehicle groups respectively (p=0.180).

- The percentage of responders for a symptom, defined as patients with at least 7.3 points improvement in OSDI at baseline between 23 and 32 AND a 13.4 points improvement in OSDI in patients with baseline OSDI ≥33, was 49.22% vs. 37.29% at Day 168 for the NOVA22007 and Vehicle groups respectively (p=0.074).
- The percentage of responders on both sign (defined as patients with at least 2 grades improvement in corneal fluorescein staining on the modified Oxford scale) and symptom (defined as patients with at least 30% improvement in OSDI) was 19.53% vs. 10.17% at Day 168 for the NOVA22007 and Vehicle groups respectively (p=0.049).
- The percentage of responders on both sign (defined as patients with at least 2 grades improvement in corneal fluorescein staining on the modified Oxford scale) and symptom (defined as patients with at least 7.3 points improvement in patients with OSDI at baseline between 23 and 32 AND 13.4 points improvement in OSDI in patients with OSDI at baseline ≥33) was 21.09% vs. 9.32% at Day 168 for the NOVA22007 and Vehicle groups respectively (p=0.013).

Post-hoc analyses were also performed on a subset of patients (43 treatment, 42 control) with severe dry eye disease, i.e., corneal fluorescein staining grade 4 at baseline These analyses showed the superiority of NOVA22007 over Vehicle in the most severely affected population. Statistically significant between-group differences in favour of NOVA22007 were observed in corneal fluorescein staining, lissamine green staining, Schirmer's tear test score (without anaesthesia), percentage of responders on corneal fluorescein staining, as well as percentage of patients with improvement in both a sign (improvement in CFS) and a symptom (improvement in OSDI score), i.e., in the same patient. Specifically, the following results were observed:

- Mean change in corneal fluorescein staining from Baseline to Day 168 was -1.47 (NOVA22007) and -0.69 (Vehicle) (p=0.002, ANCOVA model).
- Mean change in lissamine green staining of the interpalpebral conjunctiva from Baseline to Day 168 was -2.31 (NOVA22007) and -0.73 (Vehicle) (p=0.003, ANCOVA model).
- Mean change in Schirmer's tear test from Baseline to Day 168 was 1.51 and -0.02 mm/5 min for the NOVA22007 and Vehicle groups, respectively (p=0.047, ANCOVA model).
- The percentage of responders (defined as patients with at least 2 grades improvement in corneal fluorescein staining on the modified Oxford scale) was 44.19% vs. 19.05% at Day 168 for the NOVA22007 and Vehicle groups respectively (p=0.011).
- The percentage of responders on both sign (defined as patients with at least 2 grades improvement in corneal fluorescein staining on the modified Oxford scale) and symptom (defined as patients with at least 13 points improvement on OSDI) was 23.26% vs. 4.76% at Day 168 for the NOVA22007 and Vehicle groups respectively (p=0.015).
- The percentage of responders on both sign (defined as patients with at least 2

grades improvement in corneal fluorescein staining on the modified Oxford scale) and symptom (defined as patients with at least 30% improvement on OSDI) was 32.56% vs. 7.14% at Day 168 for the NOVA22007 and Vehicle groups respectively (p=0.003).

In patients with corneal fluorescein staining equal to 2 at baseline (83 patients in the NOVA22007 group and 93 in the Vehicle group), the percentage of complete responders (i.e. corneal fluorescein staining score of zero on the modified Oxford scale) was 7.23% vs. 4.30% at Day 28, 16.87% vs. 7.53% at Day 84, and 21.69% vs. 10.75% at Day 168 for the NOVA22007 and Vehicle groups respectively, with a statistically significant difference in favour of the NOVA 22007 group at Day 168 (p=0.028).

LOCAL OCULAR TOLERANCE:

A reduction was observed in the percentage of patients with ocular discomfort related to study medication instillation from Baseline (NOVA22007 [54.5%] vs. Vehicle [30.0%]) to Day 168 (NOVA22007 [40.5%] vs. Vehicle [16.8%]). At Day 168, 8/242 patients (3.3%) in the NOVA22007 group and 1/250 patients (0.4%) in the Vehicle group presented ocular discomfort related to the study medication instillation; the majority of them had mild symptoms which generally lasted ≤15 minutes.

Slit lamp examinations showed fewer patients in both treatment groups with moderate or severe lid erythema, lid edema, conjunctiva erythema, conjunctiva edema, and tear film debris at Day 168 as compared to Baseline. Similar results were shown in both eyes.

SAFETY RESULTS:

Overall, 170/492 patients (34.6%) experienced 335 treatment-emergent ocular AEs during the study. The most frequent ocular AEs were eye irritation (51/335 or 15.2%), eye pain (32/335 or 9.5%), instillation site irritation (32/335 or 9.5%), meibomianitis (29/335 or 8.6%), and lacrimal disorder (25/335 or 7.4%). The incidence of ocular AEs was higher in the NOVA22007 group (42.6% vs. 26.8%). The incidence of mild and moderate ocular AEs was comparable between the treatment groups, however the incidence of severe ocular AEs was higher in the NOVA22007 group (34.7% vs. 16.0%). The incidence of definitely related (18.6% vs. 2.8%) and probably related (9.5% vs. 2.4%) ocular AEs was also higher in the NOVA22007 group.

The incidence of withdrawals due to an ocular AE was slightly higher in the NOVA22007 group (9.9% vs. 7.2%).

There were 22 SAEs of which only one was considered by the Investigator to be definitely related to the study drug (NOVA22007). This SAE consisted of severe epithelial erosion of the cornea which resolved without sequelae.

There was no change in BCVA or IOP in either treatment group (NOVA22007 or Vehicle) over the course of the study.

The majority of patients showed no systemic absorption of CsA. At Day 168, only 4/85 patients (4.7%) had a quantifiable level of blood CsA (0.102, 0.110, 0.123 and 0.155 ng/mL) with values showing that the systemic absorption of CsA was negligible (Lower Limit of Quantification [LLOQ] = 0.10 ng/mL).

Patients in the NOVA22007 had reduced HLA-DR expression, considered as a hallmark

of conjunctival inflammation, whereas there was almost no effect on HLA-DR expressions in the Vehicle group over a 6-month treatment period: At Day 168, the mean change from Baseline was -50895.7 AUF in the NOVA22007 group and -1191.9 AUF in the Vehicle group.

CONCLUSIONS:

A statistically and clinically significant improvement in corneal fluorescein staining (co-primary endpoint) was shown in the NOVA22007 group in comparison to Vehicle treatment (p=0.009) and was confirmed in all the supportive analyses.

Improvement in corneal staining in patients receiving NOVA22007 was apparent as early as Month 1 of treatment and achieved a statistical significance at Month 1, Month 3 and Month 6.

Post hoc analyses underscored the greater efficacy of NOVA22007 in the most severe patients, i.e., patients with baseline grade 3 and 4 on the modified Oxford scale and with OSDI score $\geq$ 23 at baseline, a challenging patient subgroup of eyes at risk for irreversible damage to the ocular surface, and in particular, to the cornea. The post-hoc analysis also showed greater efficacy of NOVA22007 compared to Vehicle in complete corneal clearing of fluorescein staining in the subgroup of patients with a staining equal to 2 at baseline.

With regards to symptoms, besides the improvement observed in global ocular discomfort score, the percentage of responders (patients with an improvement of 25% or greater) was statistically significantly greater in the active treatment group at Month 6 when compared to the Vehicle. No statistically significant difference was shown for global score of ocular discomfort unrelated to study medication instillation (VAS) (co-primary endpoint) since noticeable improvement was observed in both groups.

.Local ocular tolerability results were consistent with the expected ocular tolerance of CsA in this patient population and were good. This was illustrated by the good compliance observed in the study. Overall, NOVA22007 was found to be safe in this study. As expected, a higher incidence of ocular AEs was shown compared to the Vehicle; nonetheless there was no decrease in visual acuity, no effect on intraocular pressure or vital signs, and no systemic absorption of CsA in the vast majority of patients treated during the course of the study.

In conclusion, NOVA22007 with once-daily dosing was shown to be safe and effective for the treatment of dry eye disease. Efficacy was observed as early as one month and was maintained during the 6 months of the study. This is the first time a consistent clinical effect on the keratitis associated with dry eye was evidenced in an adequately-controlled study.

Date of the report: 10 August 2010