Synopsis

Title of the study: **Efficacy and Safety assessment of T4020 *versus* vehicle in patients with chronic neurotrophic keratitis or corneal ulcer.**

Clinical phase: III.

Methodology: Multicentre, international, randomised, double-masked, 2 parallel groups *versus* vehicle in 124 evaluable patients treated for 28 days.

Statistical Method: Superiority analysis

Test product: T4020 (CACICOL20®)
1 drop into the pathologic eye once daily every 2 days for 28 days.

Reference product: Vehicle (T4020 Vehicle eye drops)
1 drop into the pathologic eye once daily every 2 days for 28 days.

Wash-Out: Patient must be willing to discontinue their current treatment (*) 7 days prior to Day 0, in order to determine the pathology's eligibility. Patient will instil preservative free artificial tears (NaCl 0.9%): one drop into the pathologic eye at least three times daily for 7 days.

(*) except for patients who need a topical ocular treatment by cyclosporine (preservative free), which will be continued throughout the study.

Number of patients: 124 evaluable patients.
Taking into account about 10% of drop-outs, a total of 138 patients should be enrolled in the study.

International Investigator Coordinator: Professor Beatrice COCHENER.

Countries: Austria, Belgium, Denmark, England, Finland, France, Greece, Italy, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, and Turkey.

Planned schedule:
Planned initiation: June 2012
Planned completion of clinical phase: March 2017.

Objectives: To assess the efficacy and safety of CACICOL20® on corneal healing *versus* vehicle following once daily every 2 days treatment for 28 days.

Primary objective: - Reduction of 50% or more in keratitis/ulcer area from baseline assessed at Day 28.

Secondary efficacy criteria

- Complete corneal healing at Day 28.
- Partial response at Day 28 defined as a reduction in the ulcer/keratitis area of 75% or more.
- Partial Response (50%) at Day 28 defined by investigator judgment.
- Complete corneal healing at Day 28 defined by investigator judgment.
- Complete corneal healing at Day 7, Day 14 and Day 21.
- Partial response at Day 7, Day 14 and Day 21 defined as a reduction in the ulcer/keratitis area of 75% or more.
- Partial response at Day 7, Day 14 and Day 21 defined as a reduction in the ulcer/keratitis area of 50% or more.
- Partial Response (50%) at Day 7, Day 14 and Day 21 defined by investigator judgement.
- Complete corneal healing at Day 7, Day 14 and Day 21 defined by investigator judgement.
- Corneal ulcer/keratitis depth assessment at Day 7, Day 14, Day 21 and Day 28.
- Corneal affected layers assessment at Day 7, Day 14, Day 21 and Day 28.
- Corneal substance loss assessment at Day 28.

Secondary clinical safety criteria

- Best corrected visual acuity at Day 28.
- Global tolerance assessed by the investigator at Day 7, Day 14, Day 21 and Day 28.
- Global tolerance assessed by the patient at Day 7, Day 14, Day 21 and Day 28.
- Adverse events recorded from Day 0 and throughout the study.
- Ocular pain assessment with the Visual Analog Scale.
- Use of analgesics treatments.

Inclusion and non-inclusion criteria for all the patients:

Inclusion Criteria:

Patients will be eligible for inclusion if all these criteria are respected:

At Selection Visit:

- Signed and dated informed consent,
- Male or female aged ≥ 18 years,
- Patient with **one chronic neurotrophic keratitis** or **one chronic neurotrophic corneal ulcer** defined by:
    - A maximal depth ≤ 2/3 of the stroma
    - A partial or complete corneal anaesthesia

At Inclusion Visit:

- No improvement of the **chronic neurotrophic keratitis** or **chronic neurotrophic corneal ulcer** after 7 days with preservative free lachrymal substitute treatment (NaCl 0.9%).

Non-inclusion criteria:

Patients fulfilling at the selection visit ONE OR MORE of the following non-inclusion criteria will not be included in the study:

Ophthalmic non-inclusion criteria

In the affected eye:

- Risk of immediate perforation of corneal ulcer.
- Descemetocele.
- Perforated corneal ulcer.
- Corneal abscess.

In the controlateral eye:

- Best far corrected visual acuity ≤ 1/10.

In both eyes:

- Active ocular infection.
- Glaucoma/ocular hypertension.

Systemic/non ophthalmic non-inclusion criteria

- General history judged by the investigator to be incompatible with the study (life-threatening patient condition).
- Known allergic hypersensitivity history to one of the components of the study medications or to test products.

Specific non-inclusion criteria for women

- Pregnancy, lactation.
- Childbearing women without an effective method of contraception (oral contraceptive, intra-uterine device, subcutaneous contraceptive implant, vaginal ring) or women not hysterectomised, menopaused or surgically sterilised.

Non-inclusion criteria related to general conditions

- Inability of patient and/or relatives to understand the study procedures and thus inability to give informed consent.
- Non-compliant patient and/or relatives (e.g. not willing to attend the follow-up visits, way of life interfering with compliance).
- Participation in another clinical study within the last 3 months.
- Already included once in this study.
- Ward of court.
- Patient not covered by the Social Security scheme (For France).

Non-inclusion criteria related to previous and concomitant medications / non-product therapies

Patient using any of the following previous and concomitant medication / treatment (according to the described periods) will not be included in the study:

CONCOMITANT MEDICATIONS / NON PRODUCT THERAPIES NOT ALLOWED BEFORE AND DURING THE STUDY		
Before the selection visit 7 days	Wash-out period 7-9 days	Treatment period
Any plan or predicable change in dose regimen for the following systemic treatments (anti-inflammatory drugs, psychotropic drugs)		
Contact lenses wear		
	Any topical ocular treatments except allowed treatments (*) (**)	
	Any systemic steroids treatment	

(*) Patient needing a topical ocular treatment by cyclosporine (preservative free) will continue this treatment at the same dose regimen throughout the study.
(**) Patient will instil preservative free artificial tears: NaCl 0.9% 3 to 8 times daily.

Sub-group of patients with ulceration/ulcer:

Patients will be eligible for inclusion if ALL above criteria and the additional non-inclusion criterion below are respected:

- Stage 1 neurotrophic keratitis according to the Mackie classification, in the affected eye.

Visit schedule:

- ✓ Selection visit: Day-9/ Day-7,
- ✓ Inclusion visit: Day 0,
- ✓ Follow-up visit: Day 7 / Day 9,
- ✓ Follow-up visit: Day 14 (± 1 day),
- ✓ Follow-up visit: Day 21 (± 2 days),
- ✓ Final visit: Day 28 (± 3 days).

According to the investigator's decision, from Day 7 and to the end of the study:

- in case of improvement or stable status of the neurotrophic keratitis/corneal ulcer, the patient may continue the study.
- in case of aggravation of the neurotrophic keratitis/corneal ulcer, the patient may stop the study.

In case of withdrawal from the study, the investigator will prescribe the best appropriate treatment to the patient.

Data Monitoring Committee (DMC) and Interim analyses:

This Data Monitoring Committee will be composed of 4 members: 3 ophthalmologists: Pr. Christophe BAUDOUIN, Pr Gerd GEERLING, Pr Kostas BOBORIDIS and an expert statistician: Pr. Jean-Marie GROUIN. They will review all patient data as study progresses.

Two interim analyses are planned when 50 patients and 88 patients will be included. Both interim analyses could allow for early claim efficacy according to pre-specified rules. The DMC may also recommend stopping the study in case of evidence of unexpected major safety issues. DMC responsibilities and decision rules for stopping the trial are specified in a DMC charter.

Independent Masked Adjudication Committee:

This Independent Masked Adjudication Committee will be composed of 3 independent corneal specialists: Pr Antoine Labbé, Dr Serge Doan, Pr Eric Gabison.
They will review data currently collected in Study LT4020-PIII-12/11, to define presence or absence of neurotrophic corneal ulceration/ulcer.
They will estimate the number of patients currently included with no ulcer/ulceration.

Study Follow-up:

At the day 28 visit, in case of improvement, without complete healing, of the chronic neurotrophic keratitis or chronic neurotrophic corneal ulcer, and according to the investigator's judgment, a six-month follow-up (or till healing before this delay) should be done by the investigator in order to collect data on the evolution of the keratitis/ulcer. During this follow-up, the patient will instil CACICOL20® at the same dose regimen, i.e. 1 drop into the pathologic eye once daily every 2 days. All details will be defined in the ancillary protocol.

These data will be integrated in the clinical study report.

Statistical Considerations:

The primary efficacy endpoint will be the response defined as the reduction of 50% or more in keratitis/ulcer area from baseline assessed at Day 28.

The primary efficacy analysis will be conducted in the modified Intent-To-Treat Set using the Fisher's exact test at the 0.025 one-sided significance nominal level. Missing data will be handled using the Last Observed Carried forward technique. Multiple Imputation Methods will be performed to investigate the robustness of results.

The main secondary efficacy endpoints will be the complete response and the partial response (defined as the reduction of 75% or more in the ulcer/keratitis area) assessed at Day 28 and analysed like the primary endpoint.

Time to response will be analysed by the Kaplan-Meier method and groups will be compared by the Log-rank test.

Safety variables will be described and analysed according to usual statistical methods.

Sample Size Considerations

The sample size determination is based on the primary efficacy endpoint, i.e. the response defined as the reduction of 50% or more in keratitis/ulcer area from baseline assessed at Day 28.

Based on an expected vehicle responder rate of 20% and a difference in rates of at least 30% with T4020 compared to vehicle, 124 evaluable patients maximum (62 per group) are needed to achieve at least a 90% power using a one-sided Fisher's exact test at the 0.025 one-sided significance nominal level.

FLOW CHART: Study investigations are to be conducted as per the following schedule of study procedures:

Study procedure	***Day -9 / Day -7*** **Visit 1 Selection Visit**		***Day 0*** **Visit 2 Inclusion Visit**	***Day 7 / Day 9*** **Visit 3 Follow-up Visit**	***Day 14 (± 1 day)*** **Visit 4 Follow-up Visit**	***Day 21 (± 2 days)*** **Visit 5 Follow-up Visit**	***Day 28 (± 3 days)*** **Visit 6 Final Visit**
Informed consent	X	**Wash-out period with preservative free artificial tears NaCl 0.9%**					
Demography	X						
Ocular medical and surgical history	X						
Systemic medical and surgical history	X						
Verification of inclusion and non-inclusion criteria / Status of the patient	X		X				
Previous and concomitant ocular/non ocular treatments	X		X	X	X	X	X
Ocular symptoms	X		X	X	X	X	X
Best corrected visual acuity in both eyes (near and far)	X		X	X	X	X	X
Slit Lamp examination + Fluorescein test	X		X	X	X	X	X
Corneal sensitivity assessment (by the aesthesiometer)	X		X				X
Ulcer/Keratitis assessment(*)	X		X	X	X	X	X
OCT examination (**)	X		X	X	X	X	X
IOP measurement on both eyes (non-contact tonometry)	X		X		X		X
Ocular pain assessment (VAS)	X		X	X	X	X	X
Dispensation of the treatment for the wash-out period	X						
Dispensation of the study drug			X		X		
Adverse events			X	X	X	X	X
Global efficacy assessment by the investigator				X	X	X	X
Global tolerance assessment by the investigator				X	X	X	X
Global tolerance assessment by the patient				X	X	X	X
Selection treatment compliance			X				
Study treatment compliance				X	X	X	X

(*) The ulcer/keratitis area should be assessed by measuring the longest linear diameter and the greatest perpendicular width using calliper and by photo.
The ulcer/keratitis evolution should be assessed by: $r = (L \times l)$ at D_n / $(L \times l)$ at D0 where L denotes the longest linear diameter and l the greatest perpendicular width.

(**) The ulcer/keratitis depth should be assessed by OCT.