Efficacy and Safety assessment of T4020 versus vehicle in patients with chronic neurotrophic keratitis or corneal ulcer. Phase III study, international, multicentre, randomised, double-masked, 2 parallel groups, versus vehicle, in 124 evaluable patients treated for 28 days.

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The primary objective is to show a difference in responder rates between the study product (T4020) and the vehicle : a reduction of 50% or more in keratitis/ulcer area from baseline (inclusion visit = V2 = Day 0) assessed at Day 28 (Visit 6).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Eye disorders
Study type	Interventional

Summary

ID

NL-OMON44908

Source
ToetsingOnline

Brief title
Clinical Study Protocol N° LT4020-PIII-12/11

Condition

- Eye disorders

Synonym
Chronic neurotrophische keratitis & Chronische neurotrophische corneal ulcus

Research involving
Human

Sponsors and support

Primary sponsor: LABORATOIRES THEA
Source(s) of monetary or material Support: By the Promotor : Laboratoires THEA

Intervention

Keyword: corneal Healing after 28 days, Currently no cure, Efficacity/Safety, neurotrophic keratitis / corneal ulcer

Outcome measures

Primary outcome

The primary outcome of the study is :

- Reduction of 50% or more in Keratitis/ulcer area from baseline assessed at

Day 28

Secondary outcome

The secundary outcome of the study is :

Clinical efficacy

- 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.

Ocular and systemic safety

- 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.

Study description

Background summary

Neurotrophic keratopathy is the result of partial or complete loss of nerve function in the cornea, which may result in disease of the corneal epithelium

and stroma.
The disease progresses in three stages:
Stage 1: superficial punctuate keratitis
Stage 2: acute loss of epithelium, associated with stromal oedema
Stage 3: ulceration with stromal melt and risk of corneal perforation

If the chronic corneal ulcer is still present after standard treatment, i.e., instilling preservative free tear substitutes, the
ophthalmologist often use alternative treatments, such as a bandage contact lens, autologous serum (prepared with
patient own blood) or have an operation with an amniotic membrane graft to protect the damaged cornea as a
bandage. The choice of treatment depends on the severity/stage of the disease and the time it takes for the cornea to
heal.
The time a patient remains on treatment will vary depending on the cause of the ulcer, size, location, and depth. Most corneal ulcers should improve within two to three weeks with appropriate treatment.
If the cornea becomes too thin due to a progressive ulcerative process, there is a danger that the cornea will perforate with potential loss of visions. In these cases, the patient may require an emergency surgical procedure such as corneal glue or a tectonic corneal transplant depending on the size of the perforation.
CACICOL20® has already been tested in humans in this form, and no adverse reactions have been observed. No specific toxicity has been demonstrated and clinical data suggest that it is efficacious, well tolerated and safe.
However, as with any product, an allergy reaction to one of its components may be possible.
CACICOL20® belongs to the family of regeneration agents (RGTA). RGTAs act as tissue protectors and healing agents, this has been demonstrated in vitro and in vivo.
The efficacy and tolerance profile of CACICOL20® have been demonstrated on a pilot study on patients with resistant corneal ulcers and corneal dystrophy as well as in a published clinical cases. CACICOL20® could therefore be used as an alternative therapy to amniotic membrane transplant or autologous serum in patients with severe neurotrophic ulcers, by stimulating healing in the extracellular matrix.

Study objective

The primary objective is to show a difference in responder rates between the study product (T4020) and the vehicle : a reduction of 50% or more in keratitis/ulcer area from baseline (inclusion visit = V2 = Day 0) assessed at Day 28 (Visit 6).

Study design

This is a phase III study, multicentre, international, randomised, double-masked, in 2 parallel groups versus vehicle in 124 evaluable patients treated for 28 days.
A total of 138 patients will be included in order to obtain 124 evaluable patients (62 patients in each group).
After randomisation, eligible patient will receive the Test product or the Vehicle, instilled at the dose regimen of one drop into the pathologic eye once daily every 2 days for 28 days.

All patients will attend 6 visits during the course of the study:

- Selection visit: Day-9/ Day-7, patients who meet the inclusion criteria will sign the consent form and will be randomly assigned to one of the two treatment arms: CACICOL20® or vehicle (negative control). Randomization will be centralized and stratified by center.

- Inclusion visit: Day 0 (Inclusion Visit : patients who fulfil all inclusion and non-inclusion criteria will be randomly assigned to 1 of the 2 treatments groups by central randomisation).

- 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).
and
- Control visit: : Day 14 (± 1 day) after the last study product instillation

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.

Intervention

Intervention :

- Informed Consent Form will be recovered prior the first visit (selection visit = V1)

- Questionnary during 1st visit : demography, ocular medical and surgical history, Systemic medical and surgical history, previous treatments
- Questionnaries at each visit from inclusion visit (V2) : global efficacy

assessment by the investigator, global tolerance assessment by the investigator, global tolerance assessment by the patient, current concomitant treatments, ocular symptoms.

Ophthalmological examination:
- Corrected visual acuity in both eyes (near and far)
- slit Lamp for the aera of Ulcer/Keratitis
- corneal sensitivity assessment
- clinical examination of the Ulcer/Keratitis
- Examination of the Ulcer/Keratitis deeper
- Measure of the ocular pression
- Mesure of the ocular pain

Besides the routine procedure,ophthalmological examinations will be more deepened.
Those examinations will allow a followup and then a faster care in case of necessity.

Study burden and risks

This study drug has already been tested in humans under this form, and no adverse reactions have been observed.
No specific toxicity has been demonstrated and clinical data are consistent with a very good tolerance and a high
safety.
The advantages of CACICOL20® are its innocuousness, its ease of use.
However, as with any treatment, an allergic reaction to one of its components is possible.
Artificial tears sometimes may cause minor ocular irritations.
Allergic reaction risks: as with taking any drug, there is a risk of allergic reaction. Some symptoms of allergic reactions
are: rash, wheezing, fainting, swelling around the mouth, throat or eyes, a fast pulse, sweating.
Risks linked to the dyes: with the use of orange (fluorescein) dye required for some exams, the patient may
experience some ocular irritations or allergy.
Risks linked to local anaesthesia: Fainting due to a slowed heart rate has been exceptionally reported.
Transient stinging sensation or irritation may occur upon instillation.

The possible benefit of this study is to receive the active treatment with CACICOL20®.
CACICOL20® is part of a new class of medicinal products regeneration agents which
increase the speed and
quality of repair, thereby leading to regeneration of damaged tissues.
CACICOL20® is a tissue matrix protector,

recommended to stimulate healing of chronic corneal lesions and reduce the pain associated with such conditions. It
may therefore have a beneficial effect in treating neurotrophic keratopathy or chronic neurotrophic ulcers.
The advantages of CACICOL20® are its innocuousness, its ease of use and respect of the environment.
CACICOL20® could therefore be used as an alternative therapy to amniotic membrane transplant or autologous
serum in patients with severe neurotrophic ulcers, by stimulating healing in the extracellular matrix.

After the 28days treatment, in case of improvement, without complete healing of the chronic neurotrophic keratitis or
chronic neurotrophic corneal ulcer, the ophthalmologist will continue to follow the patient for up to six months or until
healing if it occurs earlier (poststudy followup).The patient will then be offered treatment by CACICOL20® at the same posology.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

At Selection Visit (Visit 1)
- 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 and a partial or complete corneal anaesthesia;At Inclusion Visit (Visit 2)
- No improvement of the chronic neurotrophic keratitis or chronic neurotrophic corneal ulcer after 7 days with preservative free lachrymal substitute treatment (NaCl 0.9%).

Exclusion criteria

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 sterilized.;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).;CONCOMITANT

MEDICATIONS / NON PRODUCT THERAPIES NOT ALLOWED BEFORE (7 days before Visit 1) AND DURING THE STUDY
- Any plan or predicable change in dose regimen for the following systemic treatments (anti-inflammatory drugs, psychotropic drugs)
- Contact lenses wear;CONCOMITANT MEDICATIONS / NON PRODUCT THERAPIES NOT ALLOWED DURING THE STUDY
- Any systemic steroids treatment
- Any topical ocular treatments except allowed treatments (Allowed treatments = cyclosporine preservative free + free artificial tears: NaCl 0.9% 3 to 8 times daily)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-11-2013
Enrollment:	4
Type:	Actual

Medical products/devices used

Generic name:	T4020 (CACICOL20®)
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	23-09-2013
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	11-03-2014
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	10-08-2015
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	21-07-2016
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	N°GMDN 58069
CCMO	NL45759.099.13