CLINICAL STUDY REPORT SYNOPSIS
CLINICAL TRIAL I.2016.010
EUDRACT: 2016-001841-23
MARCH 2020

A multicenter, randomized, open-label, two-arms phase I/II clinical trial to asses efficacy and safety of cord blood eye drops in neurotrophic keratopathy

Sponsor: Banc de Sang i Teixits	
Product under investigation: CBED	
Study code: I.2016.10	
Study title: A multicenter, randomized, open-label, two-arms phase I/II clinical trial to asses efficacy and safety of cord blood eye drops in neurotrophic keratopathy	
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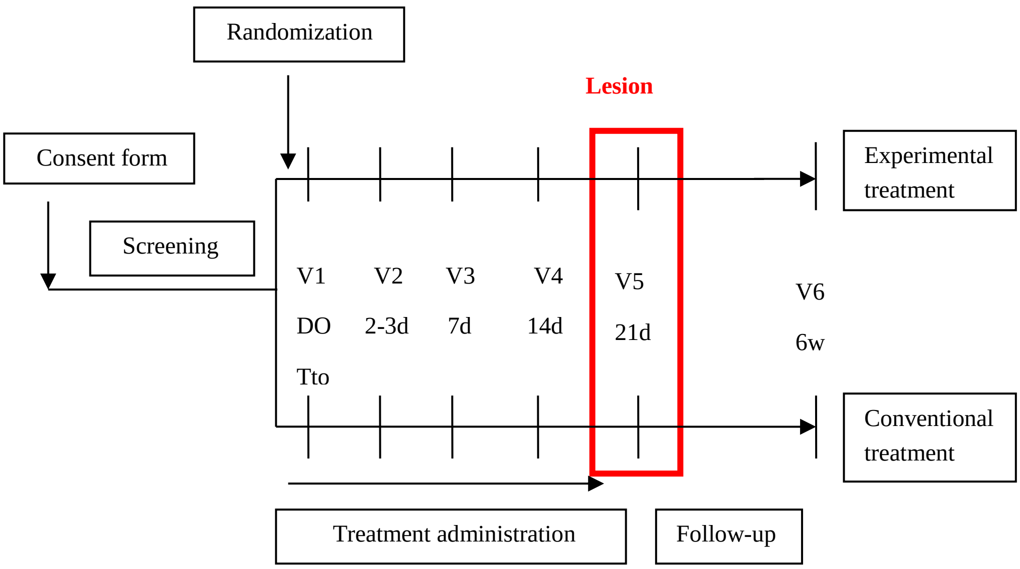
Publication (reference): does not apply	
Study Period (years): 2016-2020	**Phase:** I/II
Objectives: **<u>Main objective:</u>** To assess the efficacy of cord blood eye drops in neurotrophic keratitis (NK) treatment by changes in lesion size observed by slit lamp after 3 weeks of treatment. **<u>Secondary objectives:</u>** • To assess the safety of cord blood eye drops in NK treatment.	

- To assess the efficacy of cord blood eye drops in NK treatment by changes in lesion size observed by slit lamp after 2-3 days of treatment and at 1, 2, 3 and 6 weeks.
- To assess the corneal sensibility after 2-3 days of treatment and at 1, 2, 3 and 6 weeks.
- To assess the corneal opacity by slit lamp after 2-3 days of treatment and at 1, 2, 3 and 6 weeks.
- To assess the visual acuity after 2-3 days of treatment and at 1, 2, 3 and 6 weeks.
- To assess the NK complications per treatment group

Methodology:

This is a multicenter, randomized, open-label, two-arms phase I/II, clinical trial, in which 42 patients will be enrolled with the principal objective to evaluate the efficacy through changes in lesion size and, secondary, to evaluate the safety and efficacy through corneal sensibility, corneal opacity, visual acuity and complications of NK. Patients will be randomized 1:1 to receive experimental treatment (cord blood eye drops) or conventional treatment (artificial tears and therapeutic contact lens).



All patients, with conventional or experimental treatment, will be treated for 19 days. A topical antibiotic will be added to as a concomitant treatment to all treatment groups, until the injury closes or according to medical criteria.

After signing informed consent, inclusion and exclusion criteria will be assessed, and if the patient meets all the requirements, the patient will be randomized.

After initiation of the treatment, patients will be follow-up at 2-3 days and once a week for 3 weeks. A final follow-up is planned at 6 weeks.

Number of patients (planned and analyzed):

No. evaluable planned:	42
No. randomized and treated:	9/42
Treatment A – cord blood eye drops	5/9
Treatment B – standard	4/9
Male/Female:	6/3
Mean age (MA)	83 (±4,7)
No. analysed for efficacy:	
Full Analysis Set (FAS)	9
Population by protocol	6
No. analysed for safety:	9

Diagnosis and main inclusion criteria:

The diagnosis of stage 2 or 3 neurotrophic keratitis was made during an ophthalmologist visit by measuring the size of the ulcer, opacity, visual acuity and sensitivity.

Inclusion/exclusion criteria

Inclusion criteria:

- Age ≥ 18 years old
- NK stage 2 or 3 (Mackie classification)
- Signed Informed Consent Form
- The patient is able to understand the nature of the study and to participate throughout its duration

Exclusion criteria:

- Medical history of eye tumors
- Active eye infection
- Eyelid bad position or eyelid closure problems
- Conjunctiva scarring
- Topic chronic eye treatments with corticoids
- Acute corneal burns (<3 months)
- Intolerance to contact lens
- Allergy or inability to receive concomitant treatment with Exocin®
- Patients with immunosuppressive or chemotherapy treatment

- Pregnant woman or woman without proper contraceptive methods according to the investigator (*), or lactating women
- Participation in another clinical trial in the last month

(*) Contraceptive methods accepted in the protocol are: hormonal, intrauterine device (IUD), barrier methods, voluntary sterilization or the patient has menopause >1 year duration

Investigational drug, dose and administration schedule:

Experimental drug: cord blood eye drops

Description: eye drops plasma from cord blood diluted v/v with Plasmalyte®, without antimicrobial preservatives

Dosage regimen: 1 drop every 2 hours

Pharmaceutical form: ophthalmic preparation eye drops

Presentation: batch of 19 vials of 1 mL per vial

Route of administration: ophthalmic/ocular

Conventional treatment:

a) Artificial tears

Description: Lubristil ® (monodosis)

Dosage regimen: 1 drop every 2 hours

Pharmaceutical form: ophthalmic preparation eye drops

Presentation: batch of 20 or 30 vials of 0.3 mL per vial

Route of administration: ophthalmic

b) Therapeutic Contact lens

Description: Air Optix Night&Day

Dosage regimen: 1 contact lens per visit

Pharmaceutical form: contact lens

Presentation: 1 unit per case

Route of administration: ophthalmic/ocular

Concomitant treatment: Exocin®, 3 mg/mL eye drops solution

Description: Exocin® contains Ofloxacin 3mg/mL and Benzalkonium Chloride 0.05 mg/mL as active ingredient

Dosage regimen: 1 drop every 12 hours

Pharmaceutical form: eye drops solution

Presentation: plastic bottles 5 mL

Route of administration: ophthalmic/ocular

Study populations:

In general, tables with information on demographic variables and other relevant baseline characteristics are presented for all randomized patients. Efficacy analysis are presented for the FAS population for the safety population.

The following sets of patients will be considered:

Evaluated for selection

They are all the patients initially considered for inclusion in the study, regardless of whether they were actually included or not.

Randomized patients

They are all patients who were assigned one of the study treatments according to the randomization list.

Modified Full Analysis Set (FAS)

All randomized patients who had the main variable in the baseline evaluation (percentage of corneal ulcer closure).

Population By Protocol (PP)

All those patients considered for the mFAS population who did not present major violations of the protocol and efficacy assessments (ulcer size) are available at baseline and 3 weeks.

Safety Population

All patients who received the experimental treatment, to whom CBED was applied and all the patients who received the standard treatment, who received therapeutic contact lens, lubristil eye drops and both arms received concomitant antibiotic treatment in the form of eye drops - exocin.

Statistical methods:

Safety variables

Safety analysis were performed with the available data, without using missing data imputation techniques. None of the patients had serious adverse effects related to the experimental treatment.

Efficacy variables

Efficacy analyzes were performed with the available data, without using final data imputation techniques. The data obtained are presented using descriptive statistics.

SUMMARY OF RESULTS / CONCLUSIONS

Efficacy results:

The present study was carried out in the 10 centers (Barcelona, Girona, Terrassa, Tarragona of Spain), and included 9 patients with stage 2 and 3 neurotrophic ulcers by Mackie classification. The population was characterized by being mostly men (66%), with a mean age (SD) of 83 (± 4.7) years, with similar baseline demographic and clinical characteristics. 9 patients were randomized 5 in the Treatment A group (CBED) and 4 in the Treatment B group (standard treatment using by artificial tears and contact lens). Efficacy analyzes were performed in the mFAS population, which included 9 patients (5-CBED and 4-STD). 2/4 standard treatment patients dropped out due to lack of efficacy and were treated compassionately with CBED. One of CBED treatment group was taken out from the study due to deviation from protocol (not accomplish of exclusion criteria Nº5 Topical treatment with corticoids).

The stage of neurotrophic keratitis was analysed reduction of lesion size; improvements in visual acuity, corneal opacity on V5 (3 weeks) comparing baseline (V1, D0).

<u>mFAS population</u>: 60% of the patients in the CBED group, the lesion had completely closed in V5, while in the standard group it was 25%. 1 patient (20%) in the CBED group presented 99% closure of the lesion in V5 and completely closed in V6. 1 patient in the standard group also closed in V6.

Table 1: Results are presented for the% of patients with closure of the lesion and improvement in visual acuity, per visit in the mFAS population

	N y % of patients with ulcer closure					N y % of patients, who improved in AV				
	V2 (2-3 d)	V3 (7 d)	V4 (2 s)	**V5 (3 s)**	V6 (6 s)	V2 (2-3 d)	V3 (1 s)	V4 (2 s)	**V5 (3 s)**	V6 (6 s)
CBED n=5	0	1 (20)	2(40)	**3 (60)**	4 (80)	0	2(40)	2(40)	**3 (60)**	3 (60)
STD n=4	0	1(25)	1 (25)	**1 (25)**	2 (50)	1(25)	1(25)	1(25)	**1(25)**	1(25)

<u>The population per protocol</u>: 1 patient (25%) in the CBED group presented 99% closure of the lesion in V5 and completely closed in V6.

<u>Visual acuity</u>:

<u>mFAS</u>: 3/5 (60%) of patients improved in V5 in the experimental arm (CBED) and 1/4 (25%) in the standard arm.

<u>Population Per Protocol</u>: 3/4 (75%) of the patients improved in V5 in the group of patients in the experimental arm (CBED) and 1/2 (50%) in the standard arm.

Corneal opacity:

The mFAS population: an improvement in corneal opacity was detected in 40% (2/5) of the patients treated with CBED in V3, compared to baseline, remaining until V6. 3/5 patients had no changes in corneal opacity until V6. In the standard arm ¼ (25%) patients improved in V3 and remained until V5. And ¼ patients worsened in V3, which remained the same until V5.

The population per protocol: an improvement in corneal opacity was detected in 50% (2/4) of the patients treated with CBED in V3, compared to baseline, remaining until V6. 2/4 patients (50%) patients did not improve in corneal opacity until V5. In the standard arm 1/2 (50%) patients improved in V3 and remained until V5. And 1/2 (50%) patients worsened in V3 without detecting improvement in V5.

In **corneal esthesiometry**, no changes in V5 were observed with respect to baseline in either of the 2 treatment arms.

Safety results:

All randomized patients who received some type of treatment were included in the safety population. No AAs related to the experimental treatment were reported.

Conclusions

The small number of patients recruited does not allow for statistical analysis to make conclusions. The results are presented in a descriptive way, where we can highlight that 80% of the patients assigned to experimental treatment reach the end of the study, with a closure of the ulcer in 3/5 (60%) of the cases at three weeks (1 patient was taken out and another patient had 99% of the closed lesion at three weeks), compared to standard treatment in which 2/4 patients withdrew from the study due to lack of efficacy and 1/4 (25%) had the closed lesion at three weeks. Despite the few patients included in the study, these results suggest that treatment with CBED could be effective in this type of lesion, although an adequate sample size is required to reach this conclusion.