MULTINATIONAL, MULTICENTRE, PROSPECTIVE, LONG-TERM SAFETY AND EFFICACY FOLLOW-UP STUDY AFTER AUTOLOGOUS CULTIVATED LIMBAL STEM CELLS TRANSPLANTATION (ACLSCT) FOR RESTORATION OF CORNEAL EPITHELIUM IN PATIENTS WITH LIMBAL STEM CELL DEFICIENCY DUE TO OCULAR BURNS

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Primary Objective:To demonstrate the long term safety of one or two ACLSCT(s) in patients suffering from moderate to severe LSCD secondary to ocular burns. Secondary Objectives:• To evaluate the long-term efficacy of one or two ACLSCT(s), the degree…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Ocular injuries
Study type	Observational invasive

Summary

ID

NL-OMON49307

Source
ToetsingOnline

Brief title
HOLOCORE-FU

Condition

- Ocular injuries

Synonym
Corneal lesions with associated moderate to severe limbal stem cell defieciency due to ocular terms

Research involving
Human

Sponsors and support

Primary sponsor: Holostem Terapie Avenzate S.r.l
Source(s) of monetary or material Support: Chiesi Farmaceutica S.p.A

Intervention

Keyword: Autologous Cultivated Limbal Stem Cells Transplantation (ACLSCT), Limbal stem cell deficiency (LSCD)

Outcome measures

Primary outcome

No primary parameter; exploratory efficacy measurements (Adults only)

• Percentage of patients defined as clinically relevant *sustained success* by site investigator based on the evidence of a degree of superficial corneal neo-vascularization absent or at least invading no more than one quadrant without involvement of the central portion of the cornea AND absence of epithelial defects after staining with fluorescein. The presence of *pooling* effect will not be considered as epithelial defect.

• Percentage of patients defined as clinically relevant *sustained success* by site investigator based on overall clinical judgment.

• Degree of superficial corneal neo-vascularization evaluated by site investigator by study visit according to the number of corneal quadrants with superficial neo-vessel penetration (i.e. from 0 to 4 quadrants) and presence/ absence of central cornea invasion.

• Degree of severity of epithelial defects after fluorescein staining evaluated by site investigator by study visit according to the following four point scale: *None* = none or minimal staining; *Trace* = regional or diffuse punctate staining, pooling; *Mild* = dense coalescent staining up to 2 mm in diameter; *Severe* = dense coalescent staining >=2 mm in diameter.

• Ocular symptoms (pain, burning, photophobia). Severity of ocular symptoms (pain, burning, photophobia) evaluated using an eleven 11-point scale Numerical Pain Rating Scale (NPRS) [ranging from 0 (i.e., no symptom) to 10 (i.e., worst possible)] for Pain and by 4-point scale (None, Mild, Moderate, Severe) for Burning and Photophobia.

• Conjunctival (both limbal and bulbar) inflammation. Presence and severity of limbal and ocular inflammation will be evaluated by adoption of the Efron Grading Scale for Contact Lens Complications [ranging from normal (0) to trace (1), mild (2), moderate (3), severe (4)].

• Visual acuity evaluated as Best Corrected Visual Acuity (BCVA) from Snellen chart and expressed according to tenth scale. If patient fails to recognize letters at the 1/20 grade, visual acuity will be evaluated as the best score among the followings: finger count, hand movement, light perception or no light perception.

• Quality of Life evaluated using the composite and sub-scale scores of the National Eye Institute 25-Item Visual Function (NEI VFQ 25) and EuroQol-Five Dimensions (EQ-5D-3L) Questionnaires at each study visit. EQ-5D-Y will be adopted for pediatric patients.

• Percentage of patients defined as clinically relevant *sustained success*

after keratoplasty by site investigator based on the evidence of a degree of superficial corneal neo-vascularization absent or at least invading no more than one quadrant without involvement of the central portion of the cornea AND absence of epithelial defects after staining with fluorescein. The presence of *pooling* effect will not be considered as epithelial defect.

• Conjunctival and Corneal sensitivity and central cornea involvement

• Tear secretion measured by Schirmer*s test type I at 12 months

Safety measurements (Adults and Pediatrics):

• Treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), Adverse Event of Special Interest in accordance with the Risk Management Plan for Holoclar (AESI), including glaucoma and blepharitis

Secondary outcome

NA

Study description

Background summary

Loss of LSCD (Limbal Stem Cell Deficiency, LSCD) may be primary or secondary to systemic diseases or local injuries. Among secondary LSCD conditions, those due to ocular burns are rare,but amongst the most devastating in terms of quality of life, visual impairment, loss of work capability, and social costs.The clinical features of LSCD include pain, burning, and photophobia, chronic inflammation, tearing and -in the end- reduced or no visual acuity. Currently, there are no approved medicinal products for the treatment of this specific condition.

Various surgical corneal procedures have been attempted in the past to reconstitute the corneal surface of patients with severe LSCD. All these procedures aim at transplanting a new source of epithelium from the fellow eye

or a donor with the removal of the host*s altered one.
Among these options, autologous limbal transplantation is probably the best currently available option for ocular surface reconstruction. Nevertheless, this procedure requires a large limbal graft from the fellow eye with a potential risk of damaging the healthy eye.

Autologous Cultivated Limbal Stem Cell Transplantation (ACLSCT) is an advanced treatment for LSCD that implies the sampling of a small limbal-biopsy specimen of the fellow eye, followed by in vitro expansion to produce a cell sheet of corneal epithelium including both differentiated and stem cells. The final product is an Ophthalmic Insert consisting of an epithelial sheet of autologous corneal epithelium attached on a supportive fibrin layer in nutrient transport medium. The product is intended to be used in patients with moderate or severe LSCD secondary to chemical or physical ocular burns. After 2007, specific improvements in quality and manufacturing have been introduced to comply with the current legislation and regulations regarding Advanced Therapy Medicinal Products (ATMPs). Holoclar has been approved by EMA only recently and it is currently not marketed in any country world-wide. After the implementation of the ATMP Regulation, the autologous tissue engineered product for corneal reconstruction (now Holoclar) was nervetheless considered clinically and scientifically acceptable in Italy as a *consolidated use* therapy, and approved for reimbursement.

The results of retrospective studies with Holoclar show that after the improvements in quality and manufacturing of ACLSCT introduced after 2007, the large majority of patients with moderate to severe limbal stem-cell deficiency due to ocular burns, who received cultured limbal stem-cell grafts for corneal transplantation, achieved a positive clinical outcome with a favourable safety profile. These data are included as clinical data into the marketing authorization application (MAA) for the Tissue Engineered Product named Holoclar.The Committee for Medicinal Products for Human Use (CHMP) released positive opinion to the applicant and has recommended Holoclar, the first advanced therapy medicinal product (ATMP) containing stem cells, for approval in the European Union (EU).

The CHMP considered that Holoclar provided a first treatment option for this rare eye condition and recommended a conditional marketing authorisation because, although the data supplied by the applicant show that the medicine's benefits outweigh its risks, the data are based on retrospective studies and are not yet comprehensive. Therefore, an additional prospective study on the follow-up of the use of Holoclar should be conducted and this clinical trial has been agreed with the regulatory body in order to satisfy the need of additional and more comprehensive data obtained in a controlled setting.

Study objective

Primary Objective:

To demonstrate the long term safety of one or two ACLSCT(s) in patients suffering from moderate to severe LSCD secondary to ocular burns.
Secondary Objectives:
• To evaluate the long-term efficacy of one or two ACLSCT(s), the degree of superficial corneal neo-vascularization and corneal epithelial stability, clinical symptoms, conjunctival (both limbal and bulbar) inflammation, visual acuity, tear secretion and quality of life compared to baseline (i.e. before the first ACLSCT), long-term efficacy based on the clinical judgment of the investigator;
• To evaluate safety and clinical outcomes (i.e. superficial corneal neo-vascularization, epithelial defects, visual acuity, conjunctival inflammation, and symptoms) after keratoplasty in patients previously treated with Holoclar.

Study design

Multinational, multicenter, prospective, long-term safety and efficacy follow-up study.

It is expected that all patients who completed the HOLOCORE study - approximately 65 adults and 5 paediatric patients - will participate in the study. This study will be conducted in about 20 hospital centres in 8 European countries.

In NL this will be 4 adult patients.

The patient will have to visit the clinic every six months for a minimum of 1 year until a maximum of 5 years (depending on the time point he/she enters the FU study after having finalised the participation in the Holocore study).

Study burden and risks

The patients will have to visit the clinic every six months for a minimum of 1 year until a maximum of 5 years (depending on when entering the study after finalisation in the Holocore study)

As in the previous HOLOCORE study, some information will be collected by the medical staff during the study visits about adverse events the patients may experience and the medication the patient takes during the study (regardless the disease and the treatment of Holoclar).
Patients will also perform an ophtalmologic assessment at each visit to evaluate:
• epithelial defects by fluorescein staining;
• neo-vascularization assessment;
• Best-Corrected Visual Acuity;
• ocular tonometry;

• slit lamp examination;
• conjunctival (both bulbar and limbal) inflammation assessment;
• corneal sensitivity and central corneal involvement assessment;
• symptoms (pain, burning and photophobia);
• digital photographies of the eye for assessment of neo-vascularization;
• clinical outcome based on investigator*s judgment.

Moreover, patients will be asked to fill-in quality of life evaluation using NEI VFQ 25 and EQ-5D-3L. They are the same questionnaires already completed for the HOLOCORE study.

In case during the study the patient have to undergo a planned keratoplasty surgery, some related information will be collected and the patient will be followed-up for 12 months after the intervention.
No examination or interventional assessments will be taken for the purpose of this research.

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

All adult patients who completed the HOLOCORE core study and who consent to roll over to the present extension study at the end of the HOLOCORE follow-up.

Exclusion criteria

No specific exclusion criterion is considered for this study, except for patients dropping out from the HOLOCORE study or withdrawing consent.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-07-2019
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	04-09-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-02-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EudraCT	EUCTR2015-001344-11-NL
CCMO	NL66319.000.18