Multinational, multicentre, prospective, open-label, uncontrolled clinical trial to assess the efficacy and safety of Autologous Cultivated Limbal Stem Cells Transplantation (ACLSCT) for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns

Published: 20-08-2015
Last updated: 19-04-2024

Objectives in adult patientsPrimary Objective:To demonstrate the efficacy of Holoclar® at one year after the first treatment in patients suffering from moderate (vascularization in two-three corneal quadrants with central corneal involvement) to...

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

Summary

ID

NL-OMON50240

Source
ToetsingOnline

Brief title
HOLOCORE

Condition

- Ocular injuries

Synonym
Corneal lesions with associated moderate to severe limbal stem cell deficiency due to ocular burns

Research involving
Human

Sponsors and support

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

Intervention

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

Outcome measures

Primary outcome

ADULTS

The primary efficacy endpoint will be the percentage of patients with a success of transplantation at approximately 12 months from the first Holoclar treatment. Transplantation success is defined on the basis of the degree of *superficial corneal neo-vascularization (CNV)* and *epithelial defects*. CNV will be adjudicated by two external independent assessors on standardized, annotated pictures of patient*s eye, in a blinded fashion. The degree of *Superficial corneal neo-vascularization* will be evaluated based on the number of corneal quadrants with superficial neo-vessel penetration (i.e. from 0 to 4 quadrants) and presence/ absence of central corneal involvement.

The degree of *Epithelial defects* will be evaluated after staining with

fluorescein using the following 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.

Transplantation will be considered a clinically relevant success if the following conditions will be met:

o Superficial corneal neo-vascularization absent or at least invading no more than one quadrant without involvement of the central portion of the cornea;

AND

o Absence of epithelial defects after staining with fluorescein. The presence of *pooling* effect will not be considered as epithelial defect.

ADULT AND PAEDIATRIC PATIENTS

• Adverse Events (AEs) and treatment related adverse events (TRAEs).

• Adverse Events of Special Interest (AESI): glaucoma and blepharitis.

• Solicited ocular symptoms (pain, burning, and photophobia) occurring before Visit 11/22 (Day 90±14).

• Degree of conjunctival inflammation (i.e. limbal and bulbar conjunctival hyperaemia) occurring before Visit 11/22 (Day 90±14).

• Vital signs (blood pressure, pulse rate and respiratory rate) at baseline and in the 12-months following treatments with Holoclar.

• Haematology and blood chemistry parameters at baseline and at Visit 10/21 (Day 29±5) in the 12 months following treatments with Holoclar.

Secondary outcome

ADULTS

The key secondary efficacy variable will be the percentage of patients with clinical success after one or two ACLSCTs assessed at 12 months after the last treatment with Holoclar.

Transplantation will be considered successful on the basis of the degree of *superficial corneal neo-vascularization* and *epithelial defects* according to the same definition as for the primary efficacy endpoint assessment. Success will be adjudicated by two external independent assessors based on standardized, annotated pictures of patient*s eye, in a blinded fashion. In case of discordance in judgment between the two assessors, a final reconciled judgment must be produced.

The same slit lamp camera should be used to collect all the digital corneal slit lamp photos from a given patient throughout the study.

At all study visits during which corneal photos are to be documented the photographer will take at least 4 digital corneal slit lamp photos without fluorescein and at least 4 digital corneal slit lamp photos with fluorescein (2 photos magnification 10x, 2 photos magnification 16x).

Secondary efficacy variables

• Degree of severity of epithelial defects after fluorescein staining evaluated

by site investigator according to the same scale of the primary end-point at baseline and in the 12 months following last treatment with Holoclar;

• Degree of superficial corneal neo-vascularization evaluated by site investigator according to the same scale of the primary end-point at baseline and in the 12 months following last treatment with Holoclar;

• Presence and severity of solicited ocular symptoms (pain, burning, photophobia) evaluated using a Numerical Pain Rating Scale (NPRS) 11-point scale [ranging from 0 (i.e., no symptom) to 10 (i.e., worst possible)] and by 4-point scale (None, Mild, Moderate, Severe) at baseline and from 3 to 12 months after last treatment with Holoclar;

• Presence and severity of limbal and bulbar inflammation evaluated using the Efron Grading Scales for Contact Lens Complications [ranging from normal (0) to trace (1), mild (2), moderate (3), severe (4)] at baseline and from 3 to 12 months after last treatment with Holoclar;

• Best Corrected Visual Acuity (BCVA) from Snellen chart with values expressed according to tenth scale at baseline and in the 12 months following last treatment with Holoclar. If subject 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 Questionnaire (NEI VFQ 25) and EuroQol-Five Dimensions (EQ-5D-3L) at baseline and from 3 to 12 months after last treatment with Holoclar.

• Corneal sensitivity and involvement at baseline and in the 12-months

following last treatment with Holoclar.

CHILDREN AND ADOLESCENTS

• The degree of superficial corneal neo-vascularization will be evaluated by the assessors using the same scale and at the same timepoints as in adults;
• The degree of severity of epithelial defects will be evaluated by the assessors using the same method and at the same timepoints as for adults. Children not tolerating the fluorescein staining will be exempted.
• Presence and severity of limbal and bulbar inflammation using the same scale and at the same timepoints as in adults;
• Solicited ocular symptoms and visual acuity will be assessed by the investigator using the same method and at the same timepoints as for adults. Paediatric Snellen charts will be used in children before scholar age.
• Quality of Life evaluated using the composite and sub-scale scores of the NEI VFQ 25 and EuroQol-Five Dimensions Youth version (EQ-5D-Y) at the same timepoints as for adults.

KINDEREN EN ADOLESCENTEN

• De graad van oppervlakkige corneale neovascularisatie zal door de beoordelers worden geëvalueerd met behulp van dezelfde schaal en op dezelfde tijdspunten als bij volwassenen.

• De ernst van epitheliale defecten zal door de beoordelers worden geëvalueerd met behulp van dezelfde schaal en op dezelfde tijdspunten als voor volwassenen. Kinderen die aankleuring met fluoresceïne niet verdragen, zullen worden vrijgesteld.

• Aanwezigheid en ernst van limbale en bulbaire ontsteking met behulp van dezelfde schaal en op dezelfde tijdspunten als bij volwassenen.

• Gerapporteerde oogsymptomen en gezichtsscherpte zullen door de onderzoeker worden beoordeeld met behulp van dezelfde methode en op dezelfde tijdspunten als voor volwassenen. Bij kinderen die nog niet naar school gaan, zullen de pediatrische Snellen-kaarten gebruikt worden.

• Kwaliteit van leven, geëvalueerd met behulp van de samengestelde en subschaalscores van de NEI VFQ 25 en EuroQol-Five Dimensions Youth version (EQ-5D-Y) op dezelfde tijdspunten als voor volwassenen.

Study description

Background summary

Loss of LSC (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 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 (Holoclar) 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 nevertheless 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 LSCD, 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 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 study on 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

Objectives in adult patients

Primary Objective:
To demonstrate the efficacy of Holoclar® at one year after the first treatment

in patients suffering from moderate (vascularization in two-three corneal quadrants with central corneal involvement) to severe (four corneal quadrants with central corneal involvement) LSCD resulting in severe visual impairment and secondary to ocular burns, in terms of percentage of patients with a success of transplantation at approximately 12 months from the first Holoclar® treatment.

Key Secondary Objective:
To evaluate the efficacy of one or two treatments with Holoclar at one year after the last treatment.

Objectives in paediatric patients

To evaluate the clinical safety profile of treatment with ACLSCT, including limbal biopsy, Holoclar, transplantation procedure and post-transplantation treatment.

To explore the following efficacy parameters:
o presence of pain, burn and photophobia after the last treatment with Holoclar during follow-up;
o presence of limbal and bulbar inflammation after the last treatment with Holoclar during follow-up
o degree of severity of superficial corneal neo-vascularization and (if tolerated) of epithelial defects during follow up;
o improvement in best corrected visual acuity after the last treatment with Holoclar during follow up;
o improvement in patient*s quality of life after last treatment with Holoclar during follow up.

Study design

Multinational, multicentre, prospective, open label, uncontrolled clinical trial.

A total of 15 clinic visits (Pre-Screening Visit 0 to Visit 14) will be performed during the study, as follows:
- Pre-screening Visit/ Visit 0 (it should occur approximately within 45-15 days before Screening Visit)
- Screening / Pre-surgical Visit (Baseline Visit) / Start of roll-in phase Visit 1 (approx. Month -7 before transplantation)
- Limbal Biopsy / Roll-in phase/ Visit 2 (approx. 180 days ± 30 before transplantation)
- Roll-in phase/ Visit 3 (approx. 2 months after biopsy)
- Roll-in phase/ Visit 4 (approx. 4 months after biopsy)
- Roll-in phase/ Confirmation Visit/ Visit 5 (-13 ± 2 days before transplantation)

- Transplantation Visit/ Visit 6 (Day 1)
- Post-transplantation Visit/ Visit 7 (Day 2, day after transplantation)
- Post-transplantation Visit/ Visit 8 (Day 4 ± 1)
- Post-transplantation Visit/ Visit 9 (Day 15 ± 3)
- Post-transplantation Visit/ Visit 10 (Day 29 ± 5)
- Post-transplantation Visit/ Visit 11 (Day 90 ± 14)
- Post-transplantation Visit/ Visit 12 (Day 180 ± 14)
- Post-transplantation Visit/ Visit 13 (Day 270 ± 14)
- Post-transplantation Visit/ Visit 14 (Day 360 ± 14) (End-Point Visit).

The study duration per patient is 19 months ±15 dd

Intervention

ACLSCT includes a single administration of Holoclar through a dedicated surgical procedure of corneal surface scraping and product application under local (para- or -retrobulbar) or general anesthesia. The surgical procedure is then followed by a post-transplantation treatment with corticosteroids and antibiotics given initially per-os and then topically (4 weeks) as follow:
• After the biopsy, topical antibiotic prophylaxis with single-dose preservative-free Gentamycin Sulphate or Netilmicin Sulphate or Levofloxacin, 3-4 drops TID for 7-8 days until resolution of the surgical lesion.

• After administration of Holoclar:
o Systemic corticosteroid treatment: prednisone p.o. for 4 weeks after ACLSCT at a daily dose of 0.5 mg/kg/die for 2 weeks (maximum 25 mg/die in paediatric population), then tapered to 0.25 mg/kg/die for 1 week and to 0.125 mg/kg/die for 1 week. In case of persistent inflammation, the corticosteroid treatment might be maintained or re-introduced according with the judgement of physician.

o Systemic antibiotic treatment: doxycyclin 100 mg tablets twice daily for 2 weeks after ACLSCT. In case of contraindications to doxycyclin, amoxicillin 500 mg twice daily can be used instead. In paediatric patients, amoxicillin will be used adjusting the dose according to the age and the weight of the patient (within 40 kg body weight, amoxicillin 250 mg tablets TID or granular suspension 50 mg/kg divided in 2-3 doses; above 40 kg body weight: as per adult indication). Erythromycin will be adopted for paediatric patients in case of amoxicillin allergy (within 12 years: 200 mg tablets TID every 12 kg body weightor 50 mg/kg granular suspension divided in 2-3 doses; above 12 years: 600 mg tablets TID).

• Topical corticosteroid treatment: preservative-free dexamethasone 0.1% (or methylprednisolone 1%) eye drops for a total of 4 weeks starting from day 15: TID for 2 weeks followed by BID for 1 week and then QD for 1 week. Topical corticosteroid can be maintained in case of persistent inflammation.

• Topical antibiotic treatment: preservative-free Gentamycin Sulphate or

Netilmicin Sulphate or Levofoxacin emihydrate will be adopted in case of epithelial defect starting on day +21 after ACLSCT and maintained according with the judgment of physician.

In case of *failure* of the first procedure according to Independent Assessors* judgement at 12-month follow-up, eligible patients can undergo to a second implantation.

Study burden and risks

Patients will attend at least 15 visits at the clinic within a period of at least 19 months.
Patients will perform de undergo assessments/procedures during one of these visits:
- Physical examintation cehck, Vital signs (blood pressure, pulse rate and respiratory rate), ECG
- Four times blood sampling within 19 months (standard haematology and biochemistry and infectious assessments) + a urine pregnancy test (if applicable)
- Ophthalmologic examination
- Evaluation of pain, burning and photophobia
- Quality of life evaluation (a separate one for pediatric population)
- Digital photography of the eye
- Surgical procedure (during Visit 2, which will last about 3-4 hours) for acquisition of limbal stem cells biopsy from the contralateral eye (not affected eye), followed by a short-term local prophylactic antibiotics for 8 days.
- Surgical procedure in which the graft (ACLSCT; Holoclar®) is inserted (only visit No. 6 (duration of the visit is 3-4 hours) or visit No. 17 in case the first transplant was not successful and the patient is eligible for a second transplant). This is followed by a systemic antibiotic treatment (2 weeks), a systemic anti-inflammatory treatment (2 weeks). Subsequently, three weeks after the transplantation a superficial antibiotics and anti-inflammatory treatment will be started with a duration that is determined by the investigator.

Most side effects associated with Holoclar® are mild and disappear in the weeks after surgery.

Common (affect up to 1 in 10 patients)
• Bleeding around the site of the operation where Holoclar® was inserted
• Inflamed eyelid
• Problems with the transparent part of the eye
• Increased pressure in the eye (glaucoma)
• Eye pain
• Inflammation of the cornea

Uncommon (affect up to 1 in 100 patients)

• Eye disorders - stickiness of the eyelid, bloodshot eyes, swelling of the eye, and eye irritation
• Sensitivity to light
• Overgrowth around the implant (metaplasia)
• Infection of the eye
• The stitches break
• Fainting
• Bleeding from the eye lid skin

Furthermore, there are potential side effects of other drugs that are administered with Holoclar®. These side effects may vary depending on the exact product (antibiotic, steroid) which is used.

Based on previous studies patients will probably experience significant clinical benefits for participation in this study. There is a high probability that the disease may be partially or completely cured after treatment with Holoclar® and it is very likely that the treatment improve the symptoms. Furthermore, the disease and general state of the patient will be evaluated carefully and closely by the doctors. This will also help the doctor to prescribe more suitable medicines or to choose an adequate treatment when the study is finished and the implantation of Holoclar® would fail.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Written informed consent prior to any study-related procedures;, 2. Adult male and female patients (>=18 years old) - (Five Paediatric patients aged 2 to 17 years will be also enrolled for safety purposes only);, 3.LSCD secondary to unilateral or bilateral physical or chemical ocular burns*, with at least 1-2 mm2 of undamaged limbus to harvest stem cells for expansion in culture. LSCD will be considered for inclusion in presence of superficial neo-vascularization invading at least two corneal quadrants with evidence of central corneal (central 6 mm diameter) involvement (including corneal neo-vascularisation and corneal opacity) according to the independent assessors;, 4.Stability of LSCD, defined by a duration of disease of at least 24 months (12 months for minors) at the time of the Screening Visit and as presence of continuum epithelium as per fluorescein staining scored as none or trace; , 5. Presence of severe impairment in visual acuity defined by a score after best correction (i.e. Best Corrected Visual Acuity) equal or below 1/10 (or 20/200) at the Snellen chart (legal blindness); , 6. Absence of other clinical contraindications to ACLSC transplantation based upon investigator*s judgment;, 7. A cooperative attitude to follow up the study procedures (Caregivers in case of minors).

Exclusion criteria

1. LSCD of mild degree (i.e. below 2 quadrants of vascularization invasion), due to a recent burn (less than 24 months before screening for adults and less than 12 months before screening for minors), or secondary to medical conditions other than burns (i.e.radiotherapy);, 2. Severe ocular inflammation according to the Efron Grading Scale for Contact Lens Complications. Patient can be re-screened after appropriate treatment; , 3. Presence of eyelids malposition;, 4. Conjunctival scarring with fornix shortening;, 5. Severe tear secretion deficiency, determined by Schirmer*s test type 1 (<5 mm/ 5 min);, 6. Corneal anaesthesia and conjunctival anaesthesia or severe hypoesthesia;, 7. Active local or systemic infections at the time of screening. Patient can be re-screened after appropriate treatment;, 8. Diagnosis of local or systemic neoplastic disease;, 9. Congenital diseases (i.e., Aniridia);, 10. Bilateral

inflammatory diseases (i.e. Stevens-Johnson syndrome, phemphigoid);, 11. A pre-existing blindness precluding a functional recovery;, 12. Female subjects: pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are willing to use one or more reliable methods of contraception (e.g. oral contraceptives, IUD, tubal ligature). Reliable contraception should be maintained throughout the study. A pregnancy test in urine will be performed at screening in all women of childbearing potential, and repeated before biopsy and treatment. Any postmenopausal women (physiologic menopause defined as *12 consecutive months of amenorrhea*) or women permanently sterilized (e.g. tubal occlusion, hysterectomy or bilateral salpingectomy) may be enrolled in the study Parental control will be applied for the paediatric population when needed;, 13. Allergy, sensitivity or intolerance to concomitant drugs or excipients (Hypersensitivity to any of the excipients listed in section 6.1 or to bovine serum and murine 3T3-J2 cells);, 14; Contraindications to the local or systemic antibiotics and/ or corticosteroids foreseen by the protocol;, 15. Contraindications to the surgical procedure;, 16. Clinically significant or unstable concurrent disease or other clinical contraindications to stem cell transplantation based upon investigator*s judgment or other concomitant medical conditions affecting grafting procedure;, 17. Patients (or parents in case of paediatric subject) unlikely to comply with the study protocol or unable to understand the nature and scope of the study or the possible benefits or unwanted effects of the study procedures and treatments;, 18. Participation in another clinical trial where investigational drug was received less than 4 weeks prior to screening visit.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-10-2016

Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	20-08-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-06-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-04-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-09-2017
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-12-2020
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	EUCTR2014-002845-23-NL
CCMO	NL54419.000.15