Clinical trial results:
Multinational, multicenter, 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 (HOLOCORE-FU)

Summary

EudraCT number	2015-001344-11
Trial protocol	BE PL FR DE GB ES NL IT
Global end of trial date	31 March 2023

Results information

Result version number	v1 (current)
This version publication date	16 April 2024
First version publication date	16 April 2024

Trial information

Trial identification

Sponsor protocol code	CCD-GPLSCD01-03-FU

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Holostem Terapie Avanzate s.r.l.
Sponsor organisation address	Via G. Gottardi, 100, Modena, Italy, 41125
Public contact	Clinical Trial Department, Holostem Terapie Avanzate s.r.l., 39 0592058064, regulatory@holostem.com
Scientific contact	Graziella Pellegrini, Holostem Terapie Avanzate s.r.l., 39 0592058064, grzllpellegrini@gmail.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2023
Global end of trial reached?	Yes
Global end of trial date	31 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the long-term safety of one or two autologous cultivated limbal stem cells transplantation (ACLSCTs) with Holoclar in patients suffering from moderate to severe limbal stem cell deficiency (LSCD) secondary to ocular burns.

Protection of trial subjects:

The study was conducted in compliance with the Declaration of Helsinki (1964, last update Fortaleza 2013 and following amendments), ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice and all other applicable local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	47
EEA total number of subjects	46

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	1
Adolescents (12-17 years)	1
Adults (18-64 years)	40
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were selected among patients (adults and paediatrics) who completed the HOLOCORE core study and who consented to roll over to the present extension study at the end of the HOLOCORE follow-up.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Holoclar (Safety population)

Arm description:

All patients treated in the HOLOCORE clinical trial who consented to roll over to the present extension study at the end of the HOLOCORE were observed for a follow-up period which varied from a minimum of 12 months for the last patient to a maximum of 57 months for the first patient entered.

Arm type	Experimental
Investigational medicinal product name	Holoclar
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Living tissue equivalent
Routes of administration	Implantation

Dosage and administration details:

No by-protocol treatment was planned for this long-term follow-up study.
During the HOLOCORE follow-up study, patients underwent study visits every 6 months and at the time of study closure.

The study treatment was administered during the HOLOCORE study and consisted of a cell-based medicinal product: "ex vivo" expanded autologous human corneal epithelium containing stem cells. Each product contained an individual treatment dose with sufficient number of cells seeded on a 2.2 cm diameter fibrin support to cover the entire corneal surface. The dose of Holoclar was 79,000 - 316,000 cells/cm², corresponding to 1 cm² of product/cm² of defect.

Number of subjects in period 1	Holoclar (Safety population)
Started	47
Completed	44
Not completed	3
Death	1
Other	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	47	47	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	1	1	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	40	40	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	44.4		
standard deviation	± 16.2	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	39	39	

End points

End points reporting groups

Reporting group title	Holoclar (Safety population)

Reporting group description:

All patients treated in the HOLOCORE clinical trial who consented to roll over to the present extension study at the end of the HOLOCORE were observed for a follow-up period which varied from a minimum of 12 months for the last patient to a maximum of 57 months for the first patient entered.

Subject analysis set title	Keratoplasty Adult Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Keratoplasty Adult Safety Population comprises adult patients as described above who participated in the Holocore Follow-up study and underwent keratoplasty surgery at least 12 months after Holoclar implantation.

Subject analysis set title	Adult Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Adult Safety Population comprises all patients who were ≥18 years of age at the time of enrolment in the Holocore Main study and subsequently participated in the Follow-Up study.

Primary: Summary of Treatment-Emergent Adverse Events

End point title	Summary of Treatment-Emergent Adverse Events[1]

End point description:

According to the primary aim of this follow-up extension study, which is the evaluation of patients' long-term safety.

Please note that in this section we are presenting just the overview of the adverse events experienced by the trial participants.
Please refer to the detailed tables included on the Adverse Event Module for specifics.

End point type	Primary

End point timeframe:

From Baseline to the End of the study

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis is descriptive.

End point values	Holoclar (Safety population)	Keratoplasty Adult Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	18		
Units: Participants				
Number of TEAEs	20	13		
Number of Serious TEAEs	2	1		
Number of TRAEs	1	0		
Number of Serious TRAEs	0	0		
Number of TEAEs Leading to Study withdrawal	1	0		
Number of TEAEs with Fatal Outcome	1	0		
Number of Treatment Emergent AESIs	3	2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Success of transplantation at Day 360

End point title	Success of transplantation at Day 360
End point description: Invest. = investigator	
End point type	Other pre-specified
End point timeframe: at Day 360	

End point values	Keratoplasty Adult Safety Population	Adult Safety Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	45		
Units: Participants				
Success	12	17		
Success according to overall Invest. judgement	14	25		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Success of Transplantation by Post-Keratoplasty Visit

End point title	Success of Transplantation by Post-Keratoplasty Visit
End point description: Invest. = investigator	
End point type	Other pre-specified
End point timeframe: at Day 360	

End point values	Keratoplasty Adult Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Participants				
Success	12			
Success according to overall Invest. judgement	13			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Degree of Neo-vascularisation and Central Cornea Involvement

End point title	Degree of Neo-vascularisation and Central Cornea Involvement

End point description:

End point type	Other pre-specified

End point timeframe:

at Day 360

End point values	Keratoplasty Adult Safety Population	Adult Safety Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	45		
Units: Participants				
Number of corneal quadrants - 0	11	14		
Number of corneal quadrants - 1	1	3		
Number of corneal quadrants - 2	0	4		
Number of corneal quadrants - 3	0	3		
Number of corneal quadrants - 4	2	4		
Number of corneal quadrants - Missing	1	6		
Central Cornea (6 mm) involvement - Yes	1	5		
Central Cornea (6 mm) involvement - No	13	23		
Central Cornea (6 mm) involvement - Missing	1	6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Degree of neo-vascularisation and central corneal involvement

by Post-Keratoplasty visit

End point title	Degree of neo-vascularisation and central corneal involvement by Post-Keratoplasty visit

End point description:

End point type	Other pre-specified

End point timeframe:

at Day 360

End point values	Keratoplasty Adult Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Participants				
Number of corneal quadrants - 0	11			
Number of corneal quadrants - 1	2			
Number of corneal quadrants - 2	0			
Number of corneal quadrants - 3	0			
Number of corneal quadrants - 4	0			
Number of corneal quadrants - Missing	1			
Central Cornea (6 mm) involvement - Yes	0			
Central Cornea (6 mm) involvement - No	13			
Central Cornea (6 mm) involvement - Missing	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Degree of re-epithelialisation

End point title	Degree of re-epithelialisation

End point description:

End point type	Other pre-specified

End point timeframe:

at Day 360

End point values	Keratoplasty Adult Safety Population	Adult Safety Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	45		
Units: Participants				
None	14	25		
Trace	0	1		
Mild	0	1		
Severe	0	1		
Missing	1	6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: degree of re-epithelialisation by Post-Keratoplasty Visit

End point title	degree of re-epithelialisation by Post-Keratoplasty Visit

End point description:

End point type	Other pre-specified

End point timeframe:

At day 360

End point values	Keratoplasty Adult Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: participants				
None	13			
Trace	0			
Mild	0			
Severe	1			
Missing	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical Symptoms

End point title	Clinical Symptoms

End point description:

End point type	Other pre-specified

End point timeframe:
At Day 360

End point values	Adult Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: participants				
Presence of Photophobia: Yes	10			
Presence of Photophobia: No	18			
Presence of Photophobia: Missing	6			
Photophobia Severity: None	18			
Photophobia Severity: Mild	6			
Photophobia Severity: Moderate	3			
Photophobia Severity: Severe	1			
Photophobia Severity: Missing	6			
Presence of Burning: No	24			
Presence of Burning: Yes	4			
Presence of Burning: Missing	6			
Burning Severity: None	24			
Burning Severity: Mild	3			
Burning Severity: Moderate	1			
Burning Severity: Severe	0			
Burning Severity: Missing	6			
Presence of Pain: No	27			
Presence of Pain: Yes	1			
Presence of Pain: Missing	6			
Presence of at least one Ocular Symptoms: No	16			
Presence of at least one Ocular Symptoms: Yes	12			
Presence of at least one Ocular Symptoms: Missing	6			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical Symptoms by Post-Keratoplasty Visit

End point title	Clinical Symptoms by Post-Keratoplasty Visit

End point description:

End point type	Other pre-specified

End point timeframe:
At Day 360

End point values	Keratoplasty Adult Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: participants				
Presence of Photophobia: No	10			
Presence of Photophobia: Yes	4			
Presence of Photophobia: Missing	0			
Photophobia Severity: None	10			
Photophobia Severity: Mild	1			
Photophobia Severity: Moderate	3			
Photophobia Severity: Severe	0			
Photophobia Severity: Missing	0			
Presence of Burning: No	11			
Presence of Burning: Yes	3			
Presence of Burning: Missing	0			
Burning Severity: None	11			
Burning Severity: Mild	2			
Burning Severity: Moderate	1			
Burning Severity: Severe	0			
Burning Severity: Missing	0			
Presence of Pain: No	12			
Presence of Pain: Yes	1			
Presence of Pain: Missing	1			
Presence of at least one Ocular Symptoms: No	9			
Presence of at least one Ocular Symptoms: Yes	5			
Presence of at least one Ocular Symptoms: Missing	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: BCVA improvement

End point title	BCVA improvement
End point description: BCVA: best corrected visual acuity	
End point type	Other pre-specified
End point timeframe: At Day 360	

End point values	Adult Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: Participants	21			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: BCVA improvement by Post-Keratoplasty Visit

End point title	BCVA improvement by Post-Keratoplasty Visit

End point description:

BCVA: best corrected visual acuity

End point type	Other pre-specified

End point timeframe:

At Day 360

End point values	Keratoplasty Adult Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Participants	14			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from Baseline to the End of the Study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Holoclar (Safety population)

Reporting group description:

All patients treated in the HOLOCORE clinical trial who consented to roll over to the present extension study at the end of the HOLOCORE were observed for a follow-up period which varied from a minimum of 12 months for the last patient to a maximum of 57 months for the first patient entered.

Serious adverse events	Holoclar (Safety population)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 47 (4.26%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mediastinum neoplasm			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Suture rupture			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Holoclar (Safety population)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 47 (31.91%)		

Injury, poisoning and procedural complications Suture related complication subjects affected / exposed occurrences (all)	 3 / 47 (6.38%) 3		
Eye disorders Blepharitis subjects affected / exposed occurrences (all) Corneal epithelium defect subjects affected / exposed occurrences (all) Ocular hypertension subjects affected / exposed occurrences (all)	 3 / 47 (6.38%) 3 3 / 47 (6.38%) 3 3 / 47 (6.38%) 5		
Infections and infestations Coronavirus infection subjects affected / exposed occurrences (all)	 3 / 47 (6.38%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2017	General Substantial Amendment including alignment with main HOLOCORE (CCD-GPLSCD01-03) study procedures and administrative changes.
05 June 2020	Substantial Amendment for clinical trial Sponsorship and Holoclar Marketing Authorisation Holder transfer from Chiesi Farmaceutici S.p.A. to Holostem Terapie Avanzate S.r.l. Pharmacovigilance Contacts have been updated. The time window allowed for Keratoplasty (K) visits have been also included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported