Clinical trial results:
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 (HOLOCORE).

Summary

EudraCT number	2014-002845-23
Trial protocol	DE GB BE NL FR PL ES IT
Global end of trial date	11 March 2022

Results information

Result version number	v1 (current)
This version publication date	07 May 2023
First version publication date	07 May 2023

Trial information

Trial identification

Sponsor protocol code	CCD-GPLSCD01-03

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,
Public contact	Clinical Trial Department, Holostem Terapie Avanzate s.r.l., +39 059 2058064 , regulatory@holostem.com
Scientific contact	Graziella Pellegrini, Holostem Terapie Avanzate s.r.l., +39 059 2058064 , grzllpellegrini@gmail.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001082-PIP02-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 March 2022
Global end of trial reached?	Yes
Global end of trial date	11 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of Holoclar at one year after the first treatment in patients suffering from moderate (vascularisation in two-three corneal quadrants with central corneal involvement) to severe (vascularisation in four corneal quadrants with central corneal involvement) Limbal Stem Cell Deficiency with 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.

Protection of trial subjects:

The study was performed in compliance with the 'Declaration of Helsinki' [1964, last update Fortaleza 2013 and following amendments], International Conference of Harmonization Tripartite Guidelines Guideline for Good Clinical Practice (ICH GCP), current international and national regulations, the study protocol and its amendments and current Standard Operating Procedures (SOPs) of the participating sites, the sponsor and the company in charge of monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 17
Worldwide total number of subjects	80
EEA total number of subjects	72

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)	2
Adolescents (12-17 years)	2
Adults (18-64 years)	70
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were selected among patients suffering from moderate to severe LSCD secondary to physical or chemical ocular burns referred to the investigational sites.

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

Arm description:

All patients who consented to participate received the study treatment unless they withdrew the consent or dropped-out before biopsy or treatment implantation. Each patient received the treatment prepared using her/his limbal stem cells collected from the healthy donor eye.

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:

The study treatment consisted of a cell-based medicinal product: "ex vivo" expanded autologous human corneal epithelium containing stem cells. The treatment was administered according to the treatment protocol detailed in the product SmPC .
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. Each preparation of Holoclar was intended as a single treatment. The treatment was repeated according to the physician's prescription.
In case of failure, upon Independent Assessors' judgment, a second transplantation with Holoclar was offered within 2- 6 months from declaration of failure after first Holoclar implantation.

Number of subjects in period 1	Holoclar
Started	80
Completed	49
Not completed	31
Consent withdrawn by subject	8
Adverse event, non-fatal	4
Other	10
Contingency which do not allow grafting	1
Biopsy not adequate	5
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	80	80	
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)	2	2	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	70	70	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	41.1		
standard deviation	± 16.2	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	67	67	

End points

End points reporting groups

Reporting group title	Holoclar

Reporting group description:

All patients who consented to participate received the study treatment unless they withdrew the consent or dropped-out before biopsy or treatment implantation. Each patient received the treatment prepared using her/his limbal stem cells collected from the healthy donor eye.

Subject analysis set title	Modified Intention-to-Treat population A (mITTa)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All adult patients who underwent the ACLSCT procedure.

Subject analysis set title	Modified Intention-to-Treat population B (mITTb)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All adult patients who underwent the ACLSCT procedure excluding patients treated with out of specification grafts (sub-potent batches).

Primary: Successful transplantation at 12 months after first Holoclar treatment

End point title	Successful transplantation at 12 months after first Holoclar treatment[1]

End point description:

Incidence of success is calculated as the proportion of patients with less than 2 superficial neo-vascularization corneal quadrants, with no central corneal involvement by CNV and absence of epithelial defects (none or trace) at Day 360 ±14 days after first Holoclar treatment.
CNV: Corneal Neo-Vascularisation

End point type	Primary

End point timeframe:

At 12 months after first Holoclar treatment

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	Modified Intention-to-Treat population A (mITTa)	Modified Intention-to-Treat population B (mITTb)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	69	65		
Units: Successful transplantation Percentage				
number (confidence interval 95%)				
All patients	36.2 (25 to 49)	33.8 (23 to 47)		
Patients with Evaluable Results	37.9 (26 to 51)	35.5 (24 to 49)		
Patients (12M Visit + Evaluable results)	41 (29 to 54)	38.6 (26 to 52)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Superficial corneal neo-vascularisation

End point title	Superficial corneal neo-vascularisation
End point description: The statistical analysis is descriptive.	
End point type	Other pre-specified
End point timeframe: From baseline to Day 360 post-transplant	

End point values	Modified Intention-to-Treat population A (mITTa)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Percentage of patients				
number (not applicable)				
4 corneal quadrants - Baseline	78.3			
4 corneal quadrants - Day 360	21.3			
3 corneal quadrants - Baseline	20.3			
3 corneal quadrants - Day 360	9.8			
Central corneal involvement - Baseline	98.6			
Central corneal involvement - Day 360	31.1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Shift in central corneal class

End point title	Shift in central corneal class
End point description: The statistical analysis is descriptive.	
End point type	Other pre-specified
End point timeframe: At 12 months after first Holoclar treatment	

End point values	Modified Intention-to-Treat population A (mITTa)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Percentage of patients				
number (not applicable)				

Severe at Baseline	78.1			
Severe at Day 360	21.9			
Moderate at Baseline	21.9			
Moderate at Day 360	34.3			
Mild at Baseline	0			
Mild at Day 360	25			
None at Baseline	0			
None at Day 360	18.8			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Ocular symptoms post-transplantation

End point title	Ocular symptoms post-transplantation
End point description: The statistical analysis is descriptive.	
End point type	Other pre-specified
End point timeframe: From baseline to Day 360 post-transplant	

End point values	Modified Intention-to-Treat population A (mITTa)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Percentage of patients				
number (not applicable)				
One ocular symptom - Baseline	87.0			
One ocular symptom - Day 360	55.7			
Burning - Baseline	47.8			
Burning - Day 360	24.6			
Phtotophobia - Baseline	73.9			
Phtotophobia - Day 360	44.3			
Pain - Baseline	40.6			
Pain - Day 360	21.3			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Conjunctival inflammation post-transplantation

End point title	Conjunctival inflammation post-transplantation

End point description: The statistical analysis is descriptive.	
End point type	Other pre-specified
End point timeframe: From baseline to Day 360 post-transplant	

End point values	Modified Intention-to-Treat population A (mITTa)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Percentage of patients				
number (not applicable)				
Normal limbal hyperaemia - Baseline	30.4			
Normal limbal hyperaemia - Day 360	49.2			
Trace limbal hyperaemia - Baseline	30.4			
Trace limbal hyperaemia - Day 360	26.2			
Mild limbal hyperaemia - Baseline	23.2			
Mild limbal hyperaemia - Day 360	18.0			
Moderate limbal hyperaemia - Baseline	15.9			
Moderate limbal hyperaemia - Day 360	4.9			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: BCVA post-transplantation

End point title	BCVA post-transplantation
End point description: BCVA: Best Corrected Visual Acuity The statistical analysis is descriptive.	
End point type	Other pre-specified
End point timeframe: From the baseline to Day 360	

End point values	Modified Intention-to-Treat population A (mITTa)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: BCVA				

arithmetic mean (standard deviation)				
BCVA - Baseline	1.94 (± 0.49)			
BCVA - Day 90	1.53 (± 0.76)			
BCVA - Day 90 Change from baseline	-0.39 (± 0.55)			
BCVA - Day 180	1.47 (± 0.83)			
BCVA - Day 180 Change from baseline	-0.45 (± 0.57)			
BCVA - Day 270	1.32 (± 0.91)			
BCVA - Day 270 Change from baseline	-0.62 (± 0.69)			
BCVA - Day 360	1.30 (± 0.91)			
BCVA - Day 360 Change from baseline	-0.63 (± 0.70)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: BCVA improvement post-transplantation vs stromal scarring

End point title	BCVA improvement post-transplantation vs stromal scarring

End point description:

BCVA: Best Corrected Visual Acuity

The statistical analysis is descriptive.

End point type	Other pre-specified

End point timeframe:

At 12 months after first Holoclar treatment

End point values	Modified Intention-to-Treat population A (mITTa)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Percentage patients				
number (not applicable)				
Patients with stromal scarring - Day 29	32.7			
Patients with stromal scarring - Day 360	57.8			
Patients without stromal scarring - Day 29	50.0			
Patients without stromal scarring - Day 360	100.0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Corneal/conjunctival sensitivity and corneal opacity post-

transplantation

End point title	Corneal/conjunctival sensitivity and corneal opacity post-transplantation

End point description:

The statistical analysis is descriptive.

End point type	Other pre-specified

End point timeframe:

From Baseline to Day 360

End point values	Modified Intention-to-Treat population A (mITTa)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Percentage of patients				
number (not applicable)				
Normal corneal sensitivity - Baseline	37.7			
Normal corneal sensitivity - Day 360	44.3			
Corneal hypoesthesia - Baseline	62.3			
Corneal hypoesthesia - Day 360	45.9			
Corneal opacity - Baseline	100			
Corneal opacity - Day 360	95.1			
Corneal anesthesia - Baseline	4.3			
Corneal anesthesia - Day 360	9.8			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in NEI VFQ-25 score

End point title	Change in NEI VFQ-25 score

End point description:

The National Eye Institute 25-Item Visual Function Questionnaire questionnaire (NEI VFQ) measured the dimensions of self-reported vision-targeted health status that were most important for people who had chronic eye diseases.
It consisted of a base set of 25 vision targeted questions representing 11 vision-related constructs as follows: global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and colour vision, and ocular pain.
Additionally, the VFQ-25 contained the single general health rating question which had been shown to be a robust predictor of future health and mortality in population-based studies

The statistical analysis is descriptive.

End point type	Other pre-specified

End point timeframe:

From Baseline to Day 360

End point values	Modified Intention-to-Treat population A (mITTa)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Composite score				
arithmetic mean (standard deviation)				
Composite score - Baseline	70.1 (± 17.9)			
Composite score - Day 360	78.3 (± 15.3)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Success of transplantation as judged by Site Investigator

End point title	Success of transplantation as judged by Site Investigator
End point description: The statistical analysis is descriptive.	
End point type	Other pre-specified
End point timeframe: At 12 months after first Holoclar treatment	

End point values	Modified Intention-to-Treat population A (mITTa)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Percentage of patients				
number (not applicable)				
Successful overall outcome	77.0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Success of transplantation and LSCD as per Global Consensus guidelines

End point title	Success of transplantation and LSCD as per Global Consensus guidelines

End point description:

LSCD: Limbal Stem Cells Deficiency
SoT: Success of transplantation

The statistical analysis is descriptive.

End point type	Other pre-specified

End point timeframe:

At 12 months after first Holoclar treatment

End point values	Modified Intention-to-Treat population A (mITTa)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Percentage of patients				
number (not applicable)				
SoT - All patients	42.0			
SoT - Patients (12M Visit + Evaluable results)	50.9			
Improvement in LSCD staging	60.9			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From pre-treatment phase to the end of the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Adults
Reporting group description: -	
Reporting group title	Paediatric

Reporting group description: -

Serious adverse events	Adults	Paediatric	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 76 (15.79%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	2 / 76 (2.63%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Eye operation complication			
subjects affected / exposed	1 / 76 (1.32%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 76 (1.32%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Corneal epithelium defect			

subjects affected / exposed	3 / 76 (3.95%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal perforation			
subjects affected / exposed	1 / 76 (1.32%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal thinning			
subjects affected / exposed	1 / 76 (1.32%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye pain			
subjects affected / exposed	1 / 76 (1.32%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal inflammation			
subjects affected / exposed	1 / 76 (1.32%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess jaw			
subjects affected / exposed	1 / 76 (1.32%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 76 (1.32%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Adults	Paediatric	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 76 (57.89%)	2 / 4 (50.00%)	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	4 / 76 (5.26%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Injury, poisoning and procedural complications			
Eye operation complication			
subjects affected / exposed	2 / 76 (2.63%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Suture related complication			
subjects affected / exposed	2 / 76 (2.63%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 76 (5.26%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Eye disorders			
Eye pain			
subjects affected / exposed	11 / 76 (14.47%)	0 / 4 (0.00%)	
occurrences (all)	14	0	
Corneal epithelium defect			
subjects affected / exposed	8 / 76 (10.53%)	0 / 4 (0.00%)	
occurrences (all)	14	0	
Dry eye			

subjects affected / exposed	4 / 76 (5.26%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Ulcerative keratitis			
subjects affected / exposed	3 / 76 (3.95%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Blepharitis			
subjects affected / exposed	2 / 76 (2.63%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Cataract			
subjects affected / exposed	2 / 76 (2.63%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Corneal erosion			
subjects affected / exposed	2 / 76 (2.63%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Corneal thinning			
subjects affected / exposed	2 / 76 (2.63%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Eye irritation			
subjects affected / exposed	2 / 76 (2.63%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Photophobia			
subjects affected / exposed	2 / 76 (2.63%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Chalazion			
subjects affected / exposed	0 / 76 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Conjunctival hyperaemia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Corneal disorder			
subjects affected / exposed	0 / 76 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Eye discharge			
subjects affected / exposed	0 / 76 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Lacrimation increased			

subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0	1 / 4 (25.00%) 1	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 2 / 76 (2.63%) 2	 0 / 4 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	 0 / 76 (0.00%) 0	 1 / 4 (25.00%) 2	
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all)	 0 / 76 (0.00%) 0	 1 / 4 (25.00%) 1	
Infections and infestations Influenza subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all)	 3 / 76 (3.95%) 4 2 / 76 (2.63%) 3 0 / 76 (0.00%) 0	 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 1 / 4 (25.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2016	General Substantial #1 Included exhaustive descriptions of few study procedures not detailed in previous version, specifications of side effects and deepening of treatment risk/benefit assessment.
31 January 2017	General Substantial #2 Included deletion of an invasive assessment (impression cytology), change of IC#4 for minors (the stability of Limbal Stem Cell Deficiency (LSCD) was reduced to 12 months) and re-arrangement along the study of few assessments for efficacy evaluation (QoL questionnaires removed at V11 and opacity assessment was introduced at Visit 6 after removal of the pannus) and specification of sup-potent batches release for the so called "Last chance patient". Moreover, the involvement of the Third Independent Assessor was included as was the exclusion of some concomitant treatment during the study.
05 June 2020	General Substantial #3 Clinical trial sponsorship and Holoclar MAH transfer from Chiesi Farmaceutici S.p.A. to Holostem Terapie Avanzate S.r.l.
30 September 2020	General Substantial #4 Included swab SARS-CoV-2 (PCR) tests due to COVID pandemic

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported