Clinical trial results:
A randomized clinical trial evaluating allogeneic adipose-derived mesenchymal stem cells as a treatment of dry eye disease in Sjögren's Syndrome

Summary

EudraCT number	2020-002804-38
Trial protocol	DK
Global end of trial date	28 November 2022

Results information

Result version number	v1 (current)
This version publication date	05 October 2024
First version publication date	05 October 2024

Trial information

Trial identification

Sponsor protocol code	AMASS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04615455
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospotalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, 2100
Public contact	Michael Møller-Hansen, Department of Ophtalmology, RigshospitaletGlostrup, +45 93901230, michael.moeller-hansen@regionh.dk
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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	28 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 November 2022
Global end of trial reached?	Yes
Global end of trial date	28 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Our objective is to assess the efficacy of allogeneic adipose-tissue derived mesenchymal stem cells (ASCs) administered for lacrimal gland hypofunction in patients with ADDE due to Sjögren's syndrome

Protection of trial subjects:

This trial was conducted at Copenhagen University Hospital – Rigshospitalet, Denmark, according to the Declaration of Helsinki and the ICH-GCP Guideline. The trial was approved by the Danish Medicines Agency (EudraCT no. 2020-002804-38), the Danish National Committee on Health Research Ethics, was monitored by the GCP unit in the Capital Region of Denmark. The study participants in the present study were examined to detect adverse events (AEs) at every visit, and all events were recorded in the patient's electronic case report form (eCRF). All AEs were divided into treatment-related, procedure-related, and other reasons by the investigator. All AEs were classified as either serious or non-serious based on strictly objective definitions. The investigator reported any SAEs to the sponsor within 24 hours of detection. As there had previously been no reported serious adverse reactions (SARs) related to treatment with ASCs, any SAR was considered a potential suspected unexpected serious adverse reaction (SUSAR). The sponsor reported any SUSAR that resulted in death or was considered life-threatening to the Danish Medicines Agency within 7 days of the sponsor’s knowledge of the event. Within 8 days of this report, all relevant information regarding the sponsor’s and investigator’s follow-up on the event was reported to the Danish Medicines Agency. The sponsor reported any other SUSAR to the Danish Medicines Agency within 15 days of the sponsor’s knowledge of the event. An annual safety report regarding SARs/SUSARs and comments on the general safety of the trial was sent to the Danish Medicines Agency.
In the case of an AR, treatment and closer follow-up to address the AR were planned by the investigator and sponsor. The participants were not withdrawn from the study because of an AR.

Background therapy:

CSCC_ASC(22) is an advanced therapy investigational medicinal product (ATIMP) manufactured from abdominal adipose tissue from healthy donors. CSCC_ASC(22) builds on the product CSCC_ASC presently in phase II clinical trials for ischemic heart disease, modified to meet treatment specific dosage needs for the indication ADDE.
CSCC-ASC(22) is aseptically procured and manufactured according to tissue law and GMP at Cardiology Stem Cell Centre, Rigshospitalet (aut no 32298 and 23909), using manual isolation of cells from abdominal fat tissue, animal-free expansion in automated closed bioreactor systems and cryopreservation of the final product.
The active substance is in vitro expanded ASCs. The final product, CSCC_ASC(22), is provided as a cryopreserved suspension of 22 million ASCs per ml with a total volume of 1,3 ml per vial. The excipient is Cryostor CS10 (BiolifeSolutions), holding 10% DMSO.
All healthy donors sign informed consent complying with the declaration of Helsinki. Prior to donation donor eligibility is determined based on a donor interview, a questionnaire and testing for infectious disease markers. A donor is eligible only if the screening shows that the donor is healthy, and free from risk factors, and the laboratory tests for infectious disease agents are negative. Donor eligibility is determined and documented by two medical doctors independently. Each donor is tested for HIV, hepatitis B and C, syphilis and HTLV I/II serology by serum analysis within 30 days prior to liposuction. In addition, a blood sample is drawn on the day of donation for repeated serology and NAT (nucleic acid) testing of HIV, hepatitis B and C.
Liposuction is performed according to CSCC procedures and tissue license by a trained plastic surgeon and in full compliance with surgical procedures for sterile cosmetic surgery.
The CSCC_ASC (22) final product is tested sterile, mycoplasma- and endotoxin free. All biological raw materials used apply to European Pharmacopoeia

Evidence for comparator:

In an effort to test the isolated efficacy of ASCs, CryoStor CS10 has been designated to be the placebo treatment. CryoStor CS10 is a uniquely formulated serum-free, animal component-free, and defined cryopreservation medium containing 10% dimethyl sulfoxide (DMSO) designed to preserve cells in low temperature environments (-80°C to -196°C). CryoStor CS10 provides a safe, protective environment for cells and tissues during the freezing and thawing processes and during storage. CryoStor® CS10 is cGMP-manufactured with highest grade components. Cryostor CS10 has previously been tested as a comparator in human trials and is also used in planned future human trials.

Actual start date of recruitment	10 August 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted at the Department of Ophthalmology, Copenhagen University Hospital – Rigshospitalet, Denmark. Recruitment began in September 2020 and ended with last study participant included in August 2022.

Pre-assignment

Screening details:

40 patients with severe ADDE due to SS was recruited from the Dept. of Ophthalmology, Rigshospitalet if they were 1: eligible for the study and 2: the informed consent form was signed. Within 30 days from inclusion, the study participants were randomized to treatment with either ASCs or vehicle injection in one eye.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

If a participant fulfilled all inclusion and no exclusion criteria, they were allocated in a 1:1 ratio to injection of either allogeneic ASC product or vehicle in one eye. Treatment randomization was performed by personnel at the cell-processing unit before treatment of first patient in a double-blinded manner such that neither the participant nor the masked investigator or assessor was familiar with the allocated treatment until after the statistical analysis was performed at the end of study.

Arms

Are arms mutually exclusive?	Yes
Arm title	ASCs

Arm description:

Each participant in the ASCs group received one injection of allogeneic ASC product into the LG in one eye

Arm type	Experimental
Investigational medicinal product name	Allogeneic adipose tissue-derived stromal/stem cells
Investigational medicinal product code	CSCC_ASC(22)
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraglandular use

Dosage and administration details:

Each participant in the 2 intervention groups received one transcutaneous injection of either the allogeneic ASC product or vehicle into the LG in one eye. The injected volume corresponded to maximally 50 % of the LG volume as measured on MRI. In both intervention groups, the median injected volume of the allocated treatment was 0.18 ml, corresponding to 43 % of the median LG volume. In the ASCs group, this corresponded to a median dose of 3.96 × 106 ASCs per injection.

Arm title	Vehicle

Arm description:

Each participant in the vehicle group received one transcutaneous injection of the vehicle only, CryoStor CS10 (BioLife Solutions), into the LG in one eye. The injected volume corresponded to maximally 50 % of the LG volume as measured on MRI. Vehicle vials were stored below 180 ◦C in nitrogen dry storage until clinical use.

Arm type	Active comparator

Investigational medicinal product name	CryoStor CS10
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraglandular use

Dosage and administration details:

In both intervention groups, the median injected volume of the allocated treatment was 0.18 ml, corresponding to 43 % of the median LG volume.

Number of subjects in period 1	ASCs	Vehicle
Started	20	20
Completed	20	20

Baseline characteristics

Reporting groups	
Reporting group title	ASCs
Reporting group description:	
Each participant in the ASCs group received one injection of allogeneic ASC product into the LG in one eye	
Reporting group title	Vehicle
Reporting group description:	
Each participant in the vehicle group received one transcutaneous injection of the vehicle only, CryoStor CS10 (BioLife Solutions), into the LG in one eye. The injected volume corresponded to maximally 50 % of the LG volume as measured on MRI. Vehicle vials were stored below 180 ◦C in nitrogen dry storage until clinical use.	

Reporting group values	ASCs	Vehicle	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
Adults (18-64 years)	12	15	27
From 65-84 years	8	5	13
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	20	20	40
Male	0	0	0
Primary SS Units: Subjects			
pSS	16	18	34
sSS	4	2	6
LG volume, study eye (cm3) Units: cm3			
median	0.41	0.43	
inter-quartile range (Q1-Q3)	0.24 to 0.60	0.25 to 0.84	-

End points

End points reporting groups

Reporting group title	ASCs

Reporting group description:

Each participant in the ASCs group received one injection of allogeneic ASC product into the LG in one eye

Reporting group title	Vehicle

Reporting group description:

Each participant in the vehicle group received one transcutaneous injection of the vehicle only, CryoStor CS10 (BioLife Solutions), into the LG in one eye. The injected volume corresponded to maximally 50 % of the LG volume as measured on MRI. Vehicle vials were stored below 180 ◦C in nitrogen dry storage until clinical use.

Primary: OSDI score

End point title	OSDI score

End point description:

End point type	Primary

End point timeframe:

Change from baseline at the 12 months follow-up

End point values	ASCs	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: points				
arithmetic mean (confidence interval 95%)	-16.1 (-23.4 to -8.8)	-20.8 (-28.1 to -13.5)		

Statistical analyses

Statistical analysis title	Change in OSDI score

Statistical analysis description:

The mean of the outcome measures for each of the 2 intervention groups at each of the follow-up time points was modelled in linear mixed models. For each outcome at each follow-up time point, these models produced an estimate for the mean difference from baseline and its corresponding 95 % confidence interval (CI). Whether these differences from baseline differ between the 3 groups was assessed by simple subtraction of these models. The significance level was $p < 0.05$.

Comparison groups	ASCs v Vehicle

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [1]
Method	Mixed models analysis

Notes:

[1] - p=0.374

Secondary: NIKBUT first, study eye

End point title	NIKBUT first, study eye

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to 12 months follow-up

End point values	ASCs	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: second				
arithmetic mean (confidence interval 95%)	5.51 (2.42 to 8.59)	2.65 (-0.48 to 5.78)		

Statistical analyses

Statistical analysis title	Change in NIKBUT first, study eye
Comparison groups	ASCs v Vehicle
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [2]
Method	Mixed models analysis

Notes:

[2] - p=0.205

Secondary: Schirmer test score, study eye

End point title	Schirmer test score, study eye

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to 12 months follow-up

End point values	ASCs	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mm				
arithmetic mean (confidence interval 95%)	3.45 (0.69 to 6.21)	3.5 (0.74 to 6.26)		

Statistical analyses

Statistical analysis title	Change in Schirmer test score
Comparison groups	ASCs v Vehicle
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Tear meniscus height, study eye

End point title	Tear meniscus height, study eye

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to 12 months follow-up

End point values	ASCs	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mm				
arithmetic mean (confidence interval 95%)	-0.02 (-0.07 to 0.02)	-0.02 (-0.07 to 0.03)		

Statistical analyses

Statistical analysis title	Change in tear meniscus height
Comparison groups	ASCs v Vehicle

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [3]
Method	Mixed models analysis

Notes:

[3] - p=0.876

Secondary: Tear osmolarity, study eye

End point title	Tear osmolarity, study eye

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at the 12 months follow-up

End point values	ASCs	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mosm/L				
arithmetic mean (confidence interval 95%)	-12.4 (-24.6 to -0.12)	3.01 (-10.3 to 16.3)		

Statistical analyses

Statistical analysis title	Change in tear tear osmolarity
Comparison groups	ASCs v Vehicle
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [4]
Method	Mixed models analysis

Notes:

[4] - p=0.098

Secondary: Oxford score, study eye

End point title	Oxford score, study eye

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to the 12 months follow-up

End point values	ASCs	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: points				
arithmetic mean (confidence interval 95%)	0.15 (-0.21 to 0.51)	0 (-0.36 to 0.36)		

Statistical analyses

Statistical analysis title	Change in Oxford score
Comparison groups	ASCs v Vehicle
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [5]
Method	Mixed models analysis

Notes:

[5] - p=0.567

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All 40 participants in the intervention groups completed the follow-up 12 months after treatment.	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	5.0
Reporting groups	
Reporting group title	ASCs
Reporting group description: -	
Reporting group title	Vehicle
Reporting group description: -	

Serious adverse events	ASCs	Vehicle	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	ASCs	Vehicle	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 20 (85.00%)	13 / 20 (65.00%)	
Eye disorders			
Ocular discomfort			
subjects affected / exposed	13 / 20 (65.00%)	13 / 20 (65.00%)	
occurrences (all)	13	13	
Periorbital oedema			
subjects affected / exposed	17 / 20 (85.00%)	11 / 20 (55.00%)	
occurrences (all)	17	11	
Pain	Additional description: Pain at injections site		
subjects affected / exposed	7 / 20 (35.00%)	4 / 20 (20.00%)	
occurrences (all)	7	4	
Vision blurred			

subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	2 / 20 (10.00%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported