



## 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    | Rigshospitalet                                                                                                             |
| Sponsor organisation address | Blegdamsvej 9, Copenhagen, Denmark, 2100                                                                                   |
| Public contact               | Michael Møller-Hansen, Department of Ophtalmology, RigshospitaletGlostrup, +45 93901230, michael.moeller-hansen@regionh.dk |
| Scientific contact           | Michael Møller-Hansen, Department of Ophtalmology, RigshospitaletGlostrup, +45 93901230, michael.moeller-hansen@regionh.dk |

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:

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## 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:

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## 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:

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## 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:

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### 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  |
| <b>Arm title</b>             | 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  $3.96 \times 10^6$  ASCs per injection.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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<br>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<br>Units: Subjects    |              |              |       |
| Female                                   | 20           | 20           | 40    |
| Male                                     | 0            | 0            | 0     |
| Primary SS<br>Units: Subjects            |              |              |       |
| pSS                                      | 16           | 18           | 34    |
| sSS                                      | 4            | 2            | 6     |
| LG volume, study eye (cm3)<br>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:<br>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:<br>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:<br>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:<br>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 <sup>[1]</sup> |
| 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

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[2]</sup>             |
| 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 <sup>[3]</sup> |
| 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

|                                         |                                |
|-----------------------------------------|--------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[4]</sup>          |
| 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

| <b>End point values</b>                   | 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

| <b>Statistical analysis title</b>       | 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 <sup>[5]</sup>  |
| 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 | 2 / 20 (10.00%) | 2 / 20 (10.00%) |  |
| occurrences (all)           | 2               | 2               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported