



## Clinical trial results:

**A Danish, single centre, double-blind, randomized study evaluating allogeneic adipose tissue derived mesenchymal stromal cell therapy to reduce primary graft dysfunction after lung transplantation.**

**A phase I-II study**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-004848-30 |
| Trial protocol           | DK             |
| Global end of trial date | 10 July 2023   |

### 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 | 12.12.2019 |
|-----------------------|------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Rigshospitalet  |
| Sponsor organisation address | Blegdamsvej 9, Copenhagen, Denmark, 2100                              |
| Public contact               | Jens Kastrup, Rigshospitalet, 45 35452819,<br>jens.kastrup@regionh.dk |
| Scientific contact           | Jens Kastrup, Rigshospitalet, 45 35452819,<br>jens.kastrup@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:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 10 July 2023 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 10 July 2023 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 10 July 2023 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

To investigate safety of treatment with allogeneic adipose tissue-derived mesenchymal stromal cells (ASCs) in patients undergoing lung transplantation, to evaluate whether the treatment can reduce host immunological reaction towards the graft, and to reduce the ischemic reperfusion-injury after transplantation.

Protection of trial subjects:

The study was approved by the National Committee on Health Research Ethics, the Danish Health and Medicines Agency and the Data Inspectorate. The study responsible persons had access to health care data from the patient's records. This information was important to ensure that the patients fulfil all the protocol criteria and approvals from the authorities.

The study was monitored by the GCP-unit, Capital region of Denmark. Representatives from these authorities and the responsible for the clinical trial had access to all patient and study data. This control ensured that the clinical study was conducted in accordance with the approved protocol

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 December 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: 30 |
| Worldwide total number of subjects   | 30          |
| EEA total number of subjects         | 30          |

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  | 4  |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Ten women and 20 men were treated with 200 million ASCs (n=10), 100 million ASCs (n=10) or saline infusion (n=10). No statistically significant differences in major baseline characteristics were observed between the three groups except in forced vital capacity and quality of life activity score. Randomization was performed using an online tool.

### Pre-assignment

Screening details:

Thirty-one patients were included from December 2020 to April 2023. During transplantation, one patient developed an unexpected need for extra corporal membrane oxygenation and thus was excluded before ASC/placebo treatment according to the in- and exclusion criteria.

### Period 1

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

Blinding implementation details:

Patients were randomized in blocks of six using a web program RANDOM.ORG - List Randomizer [Internet]. <https://www.random.org/lists/>  
CSCC was responsible for the randomization code and for preparing the cell product in infusion bag, to assure blinding of the treatment for the clinical team. It was not possible to see whether it was 200 or 100 million ASCs or placebo (saline) in the prepared infusion bag.

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | ASC 200 |

Arm description:

Patients receiving 200 million ASCs

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | ASC_CSCC        |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Allogeneic 200 million ASCs

|                  |         |
|------------------|---------|
| <b>Arm title</b> | ASC 100 |
|------------------|---------|

Arm description:

Patients receiving 100 mio. ASCs

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | ASC_CSCC        |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Allogeneic 100 million ASCs

|  |                 |
|--|-----------------|
| <b>Arm title</b>                       | Placebo         |
| Arm description:                       |                 |
| Saline infusion                        |                 |
| Arm type                               | Placebo         |
| Investigational medicinal product name | Isotonic saline |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |
| Dosage and administration details:     |                 |
| Isotonic saline infusion               |                 |

| <b>Number of subjects in period 1</b> | ASC 200 | ASC 100 | Placebo |
|---------------------------------------|---------|---------|---------|
| Started                               | 10      | 10      | 10      |
| Completed                             | 10      | 10      | 10      |

## Baseline characteristics

### Reporting groups

|   |         |
|---|---------|
| Reporting group title   | ASC 200 |
| Reporting group description:<br>Patients receiving 200 million ASCs |         |
| Reporting group title   | ASC 100 |
| Reporting group description:<br>Patients receiving 100 mio. ASCs    |         |
| Reporting group title   | Placebo |
| Reporting group description:<br>Saline infusion                     |         |

| Reporting group values                             | ASC 200 | ASC 100 | Placebo |
|--|---------|---------|---------|
| Number of subjects                                 | 10      | 10      | 10      |
| Age categorical                                    |         |         |         |
| Units: Subjects                                    |         |         |         |
| In utero   |         |         |         |
| Preterm newborn infants (gestational age < 37 wks) |         |         |         |
| Newborns (0-27 days)                               |         |         |         |
| Infants and toddlers (28 days-23 months)           |         |         |         |
| Children (2-11 years)                              |         |         |         |
| Adolescents (12-17 years)                          |         |         |         |
| Adults (18-64 years)                               |         |         |         |
| From 65-84 years                                   |         |         |         |
| 85 years and over                                  |         |         |         |
| Age continuous                                     |         |         |         |
| Age in years                                       |         |         |         |
| Units: years                                       |         |         |         |
| arithmetic mean                                    | 55.5    | 59.6    | 55.6    |
| standard deviation                                 | ± 6.8   | ± 5.6   | ± 6.2   |
| Gender categorical                                 |         |         |         |
| Gender M/F   |         |         |         |
| Units: Subjects                                    |         |         |         |
| Female   | 4       | 3       | 3       |
| Male   | 6       | 7       | 7       |

| Reporting group values                             | Total |  |  |
|--|-------|--|--|
| Number of subjects                                 | 30    |  |  |
| Age categorical                                    |       |  |  |
| Units: Subjects                                    |       |  |  |
| In utero   | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 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)      | 0  |  |  |
| From 65-84 years          | 0  |  |  |
| 85 years and over         | 0  |  |  |
| Age continuous            |    |  |  |
| Age in years              |    |  |  |
| Units: years              |    |  |  |
| arithmetic mean           |    |  |  |
| standard deviation        | -  |  |  |
| Gender categorical        |    |  |  |
| Gender M/F                |    |  |  |
| Units: Subjects           |    |  |  |
| Female                    | 10 |  |  |
| Male                      | 20 |  |  |

### Subject analysis sets

|                            |              |
|----------------------------|--------------|
| Subject analysis set title | overall      |
| Subject analysis set type  | Per protocol |

Subject analysis set description:

Statistical analysis was performed using SPSS version 29 (SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean±standard deviation and categorical variables are presented as numbers and percentages. Categorical data are compared using Fisher's exact or Chi-square test as appropriate. Analysis of variances (Anova) is used to compare more than two groups for normal data distribution. A two-sided P-value of <0.05 is considered statistically significant. It was predefined in the protocol that the ASC groups would be analysed alone and combined against the placebo group.

| Reporting group values                             | overall |  |  |
|--|---------|--|--|
| Number of subjects                                 | 30      |  |  |
| Age categorical                                    |         |  |  |
| Units: Subjects                                    |         |  |  |
| In utero   |         |  |  |
| Preterm newborn infants (gestational age < 37 wks) |         |  |  |
| Newborns (0-27 days)                               |         |  |  |
| Infants and toddlers (28 days-23 months)           |         |  |  |
| Children (2-11 years)                              |         |  |  |
| Adolescents (12-17 years)                          |         |  |  |
| Adults (18-64 years)                               |         |  |  |
| From 65-84 years                                   |         |  |  |
| 85 years and over                                  |         |  |  |
| Age continuous                                     |         |  |  |
| Age in years                                       |         |  |  |
| Units: years                                       |         |  |  |
| arithmetic mean                                    | 56.9    |  |  |
| standard deviation                                 | ± 6.3   |  |  |
| Gender categorical                                 |         |  |  |
| Gender M/F   |         |  |  |
| Units: Subjects                                    |         |  |  |
| Female   | 10      |  |  |
| Male   | 20      |  |  |





## End points

### End points reporting groups

|   |              |
|---|--------------|
| Reporting group title   | ASC 200      |
| Reporting group description:<br>Patients receiving 200 million ASCs   |              |
| Reporting group title   | ASC 100      |
| Reporting group description:<br>Patients receiving 100 mio. ASCs  |              |
| Reporting group title   | Placebo      |
| Reporting group description:<br>Saline infusion   |              |
| Subject analysis set title  | overall      |
| Subject analysis set type   | Per protocol |
| Subject analysis set description:<br>Statistical analysis was performed using SPSS version 29 (SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean±standard deviation and categorical variables are presented as numbers and percentages. Categorical data are compared using Fisher's exact or Chi-square test as appropriate. Analysis of variances (Anova) is used to compare more than two groups for normal data distribution. A two-sided P-value of <0.05 is considered statistically significant. It was predefined in the protocol that the ASC groups would be analysed alone and combined against the placebo group. |              |

### Primary: PGD

|  |         |
|--|---------|
| End point title  | PGD     |
| End point description:<br>PGD was defined according to the International Society for Heart and Lung Transplantation (ISHLT) as pulmonary infiltrates and hypoxemia occurring in the first 72 hours after transplantation. PGD was graded every 24 hours during the first 72 hours after transplantation. Time started at reperfusion of the second lung.<br>PGD was analysed and graded by two independent consultants with expertise in lung transplantations and blinded to the patient's treatment status. If there was disagreement in PGD, consensus had to be reached. |         |
| End point type   | Primary |
| End point timeframe:<br>72 hours   |         |

| End point values            | ASC 200         | ASC 100         | Placebo         |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed | 10              | 10              | 10              |  |
| Units: noon unit            |                 |                 |                 |  |
| number (not applicable)     | 10              | 7               | 14              |  |

### Statistical analyses

|                            |              |
|----------------------------|--------------|
| Statistical analysis title | Per protocol |
|----------------------------|--------------|

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**Statistical analysis description:**

Statistical analysis was performed using SPSS version 29 (SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean±standard deviation and categorical variables are presented as numbers and percentages. Categorical data are compared using Fisher's exact or Chi-square test as appropriate. Analysis of variances (Anova) is used to compare more than two groups for normal data distribution. A two-sided P-value of <0.05 is considered statistically significant. It was predefined in the p

|   |                                |
|---|--------------------------------|
| Comparison groups                       | ASC 200 v ASC 100 v Placebo    |
| Number of subjects included in analysis | 30                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | < 0.05                         |
| Method                                  | Chi-squared                    |
| Parameter estimate                      | Mean difference (final values) |
| Confidence interval                     |                                |
| level                                   | 90 %                           |
| sides                                   | 2-sided                        |
| Variability estimate                    | Standard deviation             |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Final follow-up after 3 months

Adverse event reporting additional description:

Please see SAE section

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |                    |
|-----------------|--------------------|
| Dictionary name | Danish authorities |
|-----------------|--------------------|

|                    |   |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | ASC 200 |
|-----------------------|---------|

Reporting group description:

Patients receiving 200 million ASCs

|                       |         |
|-----------------------|---------|
| Reporting group title | ASC 100 |
|-----------------------|---------|

Reporting group description:

Patients receiving 100 mio. ASCs

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Saline infusion

| Serious adverse events                            | ASC 200  | ASC 100         | Placebo         |
|---|--|-----------------|-----------------|
| Total subjects affected by serious adverse events |  |                 |                 |
| subjects affected / exposed                       | 6 / 10 (60.00%)                                  | 4 / 10 (40.00%) | 5 / 10 (50.00%) |
| number of deaths (all causes)                     | 0  | 1               | 0               |
| number of deaths resulting from adverse events    | 0  | 0               | 0               |
| Cardiac disorders                                 |  |                 |                 |
| Cardiomyopathy acute                              | Additional description: Takotsubo cardiomyopathy |                 |                 |
| subjects affected / exposed                       | 1 / 10 (10.00%)                                  | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all   | 0 / 1  | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0           | 0 / 0           |
| Immune system disorders                           |  |                 |                 |
| Acute cellular rejection                          | Additional description: Acute cellular rejection |                 |                 |
| subjects affected / exposed                       | 1 / 10 (10.00%)                                  | 0 / 10 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all   | 0 / 7  | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                        |  |                 |                 |
| Gastric ulcer                                     |  |                 |                 |

|   |  |                 |                 |
|---|--|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 10 (0.00%)                                     | 0 / 10 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |  |                 |                 |
| subjects affected / exposed                     | 1 / 10 (10.00%)                                    | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |  |                 |                 |
| Death   |  |                 |                 |
| subjects affected / exposed                     | 0 / 10 (0.00%)                                     | 1 / 10 (10.00%) | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 1           | 0 / 0           |
| Pleural effusion                                | Additional description: Recurrent pleural effusion |                 |                 |
| subjects affected / exposed                     | 1 / 10 (10.00%)                                    | 1 / 10 (10.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |  |                 |                 |
| subjects affected / exposed                     | 0 / 10 (0.00%)                                     | 2 / 10 (20.00%) | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| recurrent laryngeal nervous paresis             |  |                 |                 |
| subjects affected / exposed                     | 0 / 10 (0.00%)                                     | 0 / 10 (0.00%)  | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Diaphragmatic disorder                          | Additional description: Diaphragm paralysis        |                 |                 |
| subjects affected / exposed                     | 0 / 10 (0.00%)                                     | 1 / 10 (10.00%) | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |  |                 |                 |
| Breast abscess                                  |  |                 |                 |
| subjects affected / exposed                     | 1 / 10 (10.00%)                                    | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |

|   |  |                 |                 |
|---|--|-----------------|-----------------|
| Infections and infestations                     |  |                 |                 |
| Pneumonia                                       | Additional description: pneumonia, bacterial, viral and fungal |                 |                 |
| subjects affected / exposed                     | 1 / 10 (10.00%)  | 1 / 10 (10.00%) | 1 / 10 (10.00%) |
| occurrences causally related to treatment / all | 0 / 3  | 0 / 10          | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Urosepsis                                       |  |                 |                 |
| subjects affected / exposed                     | 0 / 10 (0.00%)   | 1 / 10 (10.00%) | 0 / 10 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                     | ASC 200  | ASC 100        | Placebo        |
|---|--|----------------|----------------|
| Total subjects affected by non-serious adverse events |  |                |                |
| subjects affected / exposed                           | 1 / 10 (10.00%)                                | 0 / 10 (0.00%) | 0 / 10 (0.00%) |
| Respiratory, thoracic and mediastinal disorders       |  |                |                |
| Breast abscess  | Additional description: Please see SAE section |                |                |
| subjects affected / exposed                           | 1 / 10 (10.00%)                                | 0 / 10 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all)                                     | 1  | 0              | 0              |

**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**

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|                          |
|--------------------------|
| A small phase I/II trial |
|--------------------------|

Notes: