



## Clinical trial results:

### Efficacy and safety of 72-hour infusion of Prostacyclin (1 ng/kg/min) in patients with COVID-19 induced respiratory failure – a multicentre randomized, placebo-controlled, blinded, investigator-initiated trial

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2020-001296-33 |
| Trial protocol           | DK             |
| Global end of trial date | 26 April 2021  |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 15 June 2022 |
| First version publication date | 15 June 2022 |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | COMBAT-COVID-19 |
|-----------------------|-----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04420741 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Rigshospitalet  |
| Sponsor organisation address | Blegdamsvej 9, Copenhagen, Denmark, DK-2100   |
| Public contact               | Pär Johansson, Section for Transfusion Medicine, Capital Region Blood Bank, Copenhagen University Hospital, +45 35452030, per.johansson@regionh.dk      |
| Scientific contact           | Pär Johansson, Section for Transfusion Medicine, Capital Region Blood Bank, Copenhagen University Hospital, 35452030 35452030, per.johansson@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                       | 28 April 2022 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 26 April 2021 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 26 April 2021 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to investigate whether continuous infusion of iloprost at a dose of 1 ng/kg/min for 72-hours reduces the severity of respiratory failure in the ICU as compared to placebo.

Protection of trial subjects:

Patients included in this trial is admitted to the ICU with COVID19 requiring respiratory support, therefore these patients will receive the best possible care and monitored closely during their hospital stay.

Background therapy:

Standard of care for treatment of COVID19

Evidence for comparator:

Crystalloids are the recommended volume therapy for patients with septic. We have therefore chosen that the placebo should be saline 0.9 % (NaCl) to maintain blinding in the trial as iloprost is diluted in saline. Patients receiving placebo will receive an equal volume of fluid administered in the same way as the iloprost infusion.

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 01 May 2020 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Denmark: 80 |
| Worldwide total number of subjects   | 80          |
| EEA total number of subjects         | 80          |

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)                      | 34 |

|                     |    |
|---------------------|----|
| From 65 to 84 years | 46 |
| 85 years and over   | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patients are recruited in the periode fra June 2020 to January 2021 in one of the 5 ICU2 in the Capital Region of Denmark.

### Pre-assignment

Screening details:

Patients are subject for screening if they are 18 years old or above and admitted to an ICU with confirmed COVID19 infection requirering mechanical ventilation.

However patients can only be included if souble thrombomodulin is 4 ng/mL or above.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Overall trial (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:

The trial is double-blinded with saline 0.9 % (NaCl) as placebo to maintain blinding. iloprost is diluted in saline and therefore both solutions are colorless fluids. Patients receiving placebo will receive an equal volume of fluid administered in the same way as the iloprost infusion. The preparation of trial medication will be done by an unblinded nurse, outside the ICU's, who will be responsible for preparing the investigational drug so that it can be administered in blinded fashion.

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Intervention arm |

Arm description:

Iloprost (Ilomedin®) is a marketed product which will be administered in this trial as the IMP.

|  |                                    |
|--|------------------------------------|
| Arm type                               | Experimental                       |
| Investigational medicinal product name | Ilomedin                           |
| Investigational medicinal product code |                                    |
| Other name                             | Prostacyclin                       |
| Pharmaceutical forms                   | Solution for solution for infusion |
| Routes of administration               | Infusion                           |

Dosage and administration details:

All patients will receive 72-hour continuous infusion of either active investigational drug or placebo. Patients on active treatment will receive continuous infusion of 1.0 ng/kg/min iloprost. The infusion volume of the active investigational drug and placebo will be 72 ml per 24h.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Placebo arm |
|------------------|-------------|

Arm description:

Saline 0.9% is used as comparator

|  |                       |
|--|-----------------------|
| Arm type                               | Placebo               |
| Investigational medicinal product name | Saline 0.9%           |
| Investigational medicinal product code |                       |
| Other name                             | sodium chloride       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Infusion              |

Dosage and administration details:

All patients will receive 72-hour continuous infusion of either active investigational drug or placebo. Patients on placebo will receive continuous infusion equivalent to iloprost. The infusion volume of the active investigational drug and placebo will be 72 ml per 24h.

| <b>Number of subjects in period 1</b> | Intervention arm | Placebo arm |
|---------------------------------------|------------------|-------------|
| Started                               | 41               | 39          |
| Completed                             | 41               | 39          |

## Baseline characteristics

### Reporting groups

|   |                  |
|---|------------------|
| Reporting group title   | Intervention arm |
| Reporting group description:<br>Iloprost (Ilomedin®) is a marketed product which will be administered in this trial as the IMP. |                  |
| Reporting group title   | Placebo arm      |
| Reporting group description:<br>Saline 0.9% is used as comparator   |                  |

| Reporting group values                                | Intervention arm | Placebo arm | Total |
|---|------------------|-------------|-------|
| Number of subjects                                    | 41               | 39          | 80    |
| Age categorical<br>Units: Subjects                    |                  |             |       |
| In utero  | 0                | 0           | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                | 0           | 0     |
| Newborns (0-27 days)                                  | 0                | 0           | 0     |
| Infants and toddlers (28 days-23 months)              | 0                | 0           | 0     |
| Children (2-11 years)                                 | 0                | 0           | 0     |
| Adolescents (12-17 years)                             | 0                | 0           | 0     |
| Adults (18-64 years)                                  | 16               | 18          | 34    |
| From 65-84 years                                      | 25               | 21          | 46    |
| 85 years and over                                     | 0                | 0           | 0     |
| Gender categorical<br>Units: Subjects                 |                  |             |       |
| Female  | 11               | 16          | 27    |
| Male  | 30               | 23          | 53    |

## End points

### End points reporting groups

|   |                  |
|---|------------------|
| Reporting group title   | Intervention arm |
| Reporting group description:<br>Iloprost (Ilomedin®) is a marketed product which will be administered in this trial as the IMP. |                  |
| Reporting group title   | Placebo arm      |
| Reporting group description:<br>Saline 0.9% is used as comparator   |                  |

### Primary: Days alive without mechanical care

|  |                                    |
|--|------------------------------------|
| End point title  | Days alive without mechanical care |
| End point description:<br>Number of days alive and without mechanical ventilation in the ICU for the intention to treat population |                                    |
| End point type   | Primary                            |
| End point timeframe:<br>Number of days from baseline to dag 28   |                                    |

| End point values            | Intervention arm | Placebo arm     |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 41               | 39              |  |  |
| Units: Days                 |                  |                 |  |  |
| median (standard deviation) |                  |                 |  |  |
| Number of free days         | 16 (± 12)        | 5 (± 10)        |  |  |

### Statistical analyses

|   |                                |
|---|--------------------------------|
| Statistical analysis title                                  | Primary endpoint               |
| Statistical analysis description:<br>for the ITT population |                                |
| Comparison groups   | Intervention arm v Placebo arm |
| Number of subjects included in analysis                     | 80                             |
| Analysis specification                                      | Pre-specified                  |
| Analysis type   | other                          |
| P-value   | ≤ 0.05                         |
| Method  | Wilcoxon (Mann-Whitney)        |

### Secondary: Mortality day 28

|                 |                  |
|-----------------|------------------|
| End point title | Mortality day 28 |
|-----------------|------------------|

|  |           |
|--|-----------|
| End point description:                   |           |
| Number of deaths from baseline to day 28 |           |
| End point type                           | Secondary |
| End point timeframe:                     |           |
| At day 28                                |           |

| End point values            | Intervention arm | Placebo arm     |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 41               | 39              |  |  |
| Units: Number               |                  |                 |  |  |
| Number of deaths            | 9                | 17              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mortality day 90

|  |                  |
|--|------------------|
| End point title                          | Mortality day 90 |
| End point description:                   |                  |
| Number of deaths from baseline to day 90 |                  |
| End point type                           | Secondary        |
| End point timeframe:                     |                  |
| Day 90                                   |                  |

| End point values            | Intervention arm | Placebo arm     |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 41               | 39              |  |  |
| Units: Number               |                  |                 |  |  |
| Number of deaths            | 13               | 19              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Days alive without vasopressor day 28

|   |                                       |
|---|---------------------------------------|
| End point title   | Days alive without vasopressor day 28 |
| End point description:                                  |                                       |
| Number of days alive and without vasopressor in the ICU |                                       |
| End point type  | Secondary                             |



End point timeframe:

Number of days from baseline to dag 28

| End point values            | Intervention arm | Placebo arm     |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 41               | 39              |  |  |
| Units: Days                 |                  |                 |  |  |
| Number of free days         | 22               | 13              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Days alive without vasopressor day 90

|   |                                       |
|---|---------------------------------------|
| End point title   | Days alive without vasopressor day 90 |
| End point description:                                  |                                       |
| Number of days alive and without vasopressor in the ICU |                                       |
| End point type  | Secondary                             |
| End point timeframe:                                    |                                       |
| Number of days from baseline to dag 90                  |                                       |

| End point values            | Intervention arm | Placebo arm     |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 41               | 39              |  |  |
| Units: Days                 |                  |                 |  |  |
| Number of free days         | 84               | 59              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Days alive without renal replacement therapy day 28

|   |   |
|---|---|
| End point title                                 | Days alive without renal replacement therapy day 28 |
| End point description:                          |   |
| Number of days alive and without RRT in the ICU |   |
| End point type                                  | Secondary   |
| End point timeframe:                            |   |
| Number of days from baseline to dag 28          |   |

| End point values            | Intervention arm | Placebo arm     |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 41               | 39              |  |  |
| Units: Days                 |                  |                 |  |  |
| Number of free days         | 28               | 21              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Days alive without renal replacement therapy day 90

|   |   |
|---|---|
| End point title   | Days alive without renal replacement therapy day 90 |
| End point description:<br>Number of days alive and without RRT in the ICU |   |
| End point type  | Secondary   |
| End point timeframe:<br>Number of days from baseline to dag 90            |   |

| End point values            | Intervention arm | Placebo arm     |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 41               | 39              |  |  |
| Units: Days                 |                  |                 |  |  |
| Number of free days         | 90               | 79              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Serious adverse events

|   |                        |
|---|------------------------|
| End point title   | Serious adverse events |
| End point description:  |                        |
| End point type  | Secondary              |
| End point timeframe:<br>Number of events from baseline to dag 7 |                        |

| End point values            | Intervention arm | Placebo arm     |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 41               | 39              |  |  |
| Units: Number               |                  |                 |  |  |
| SAE                         | 1                | 5               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Serious adverse reaction

|  |                          |
|--|--------------------------|
| End point title                            | Serious adverse reaction |
| End point description:                     |                          |
| End point type                             | Secondary                |
| End point timeframe:                       |                          |
| Number of reactions from baseline to dag 7 |                          |

| End point values            | Intervention arm | Placebo arm     |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 41               | 39              |  |  |
| Units: Events               |                  |                 |  |  |
| Reactions                   | 0                | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Days alive without mechanical care day 90

|  |   |
|--|---|
| End point title  | Days alive without mechanical care day 90 |
| End point description:   |   |
| Number of days alive and without mechanical ventilation in the ICU |   |
| End point type   | Secondary                                 |
| End point timeframe:   |   |
| Number of days from baseline to dag 90                             |   |

| <b>End point values</b>     | Intervention arm | Placebo arm     |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 41               | 39              |  |  |
| Units: Days                 |                  |                 |  |  |
| Number of free days         | 77               | 13              |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

SAE and SAR are collected from baseline to day 7

Adverse event reporting additional description:

Only selected serious adverse events and serious adverse reaction are collected as these patients are severely ill. Therefore, recording of all AE and SAEs in the CRF will not add valuable information to the patient's safety in this trial and will make it difficult to distinguish the real safety signal and those signs of the significant reactions

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

### Dictionary used

|                 |      |
|-----------------|------|
| Dictionary name | none |
|-----------------|------|

|                    |   |
|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall trial |
|-----------------------|---------------|

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Only certain SAE is reported in this trial due to the severity illness of the included patients

| Serious adverse events                            | Overall trial  |  |  |
|---|--|--|--|
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 6 / 80 (7.50%)   |  |  |
| number of deaths (all causes)                     | 32   |  |  |
| number of deaths resulting from adverse events    | 0  |  |  |
| Vascular disorders                                |  |  |  |
| Bleeding  | Additional description: Bleeding events requiring more than 2 RBCs within 24 hours or ongoing bleeding |  |  |
| subjects affected / exposed                       | 2 / 80 (2.50%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 2  |  |  |
| deaths causally related to treatment / all        | 0 / 2  |  |  |
| limb ischaemia                                    |  |  |  |
| subjects affected / exposed                       | 1 / 80 (1.25%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 1  |  |  |
| Gastrointestinal ischaemia                        |  |  |  |
| subjects affected / exposed                       | 1 / 80 (1.25%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Deep vein thrombosis                              |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Cardiac disorders                               |                |  |  |
| Myocardial ischaemia                            |                |  |  |
| subjects affected / exposed                     | 1 / 80 (1.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |

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

|   |                |  |  |
|---|----------------|--|--|
| <b>Non-serious adverse events</b>                     | Overall trial  |  |  |
| Total subjects affected by non-serious adverse events |                |  |  |
| subjects affected / exposed                           | 0 / 80 (0.00%) |  |  |

## 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

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34813414>