



## Clinical trial results: Therapeutic Iloprost for the treatment of Acute Respiratory Distress Syndrome (ARDS) (the Thllo-Trial): a prospective, randomized, multicenter phase II study

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2016-003168-37   |
| Trial protocol           | DE               |
| Global end of trial date | 25 November 2022 |

### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)                              |
| This version publication date     | 03 March 2023                             |
| First version publication date    | 03 March 2023                             |
| Summary attachment (see zip file) | Adverse Events Chart (Adverse Events.PNG) |

### Trial information

#### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | Thllo |
|-----------------------|-------|

#### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | University of Tuebingen  |
| Sponsor organisation address | Hoppe Seyler Strasse 3, Tuebingen, Germany, Germany, 72076   |
| Public contact               | Intensive Care Unit, University Department of Anesthesia and intensive care, +49 70712986622, peter.rosenberger@med.uni-tuebingen.de |
| Scientific contact           | Intensive Care Unit, University Department of Anesthesia and intensive care, +49 70712986622, peter.rosenberger@med.uni-tuebingen.de |

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                       | 25 November 2022 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 18 November 2021 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 25 November 2022 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

1. Improvement of oxygenation (defined as  $paO_2/FiO_2$  ratio)

Protection of trial subjects:

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial act according to Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. This is a scientific clinical study; the German Medicines Act (AMG) §40 is applicable without restrictions according to section §42.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 05 July 2019 |
| 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 | Germany: 150 |
| Worldwide total number of subjects   | 150          |
| EEA total number of subjects         | 150          |

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)                      | 80 |
| From 65 to 84 years                       | 70 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The primary analysis population was the intention to treat the population of randomized patients and provide baseline values, except for six patients who were excluded for different reasons. 707 patients were assessed for eligibility. 150 went under randomization. 77 patients received Placebo (NaCl) and 73 received Prostacyclin.

### Pre-assignment

Screening details:

After screening and determination of eligibility, patients will be included after a maximum of 96 hours between diagnosis of ARDS and randomization.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

Blinding implementation details:

The trial was not blinded. No additional labelling was needed.

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

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

Arm description:

Investigational arm who received Iloprost Trometamol (Ventavis).

|  |                                    |
|--|------------------------------------|
| Arm type                               | Experimental                       |
| Investigational medicinal product name | Iloprost Trometamol                |
| Investigational medicinal product code |                                    |
| Other name                             | Iloprost, Ventavis                 |
| Pharmaceutical forms                   | Concentrate for nebuliser solution |
| Routes of administration               | Respiratory use                    |

Dosage and administration details:

20 µg nebulized three times per day (morning, afternoon and evening) for 5 days in addition to standard care. Standard care for patients suffering from ARDS includes lung protective ventilation strategies, prone positioning and bronchoscopy.

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

Arm description:

Placebo arm (NaCl)

|  |                                    |
|--|------------------------------------|
| Arm type                               | Placebo                            |
| Investigational medicinal product name | NaCl                               |
| Investigational medicinal product code |                                    |
| Other name                             | Sodium chloride                    |
| Pharmaceutical forms                   | Concentrate for nebuliser solution |
| Routes of administration               | Respiratory use                    |

Dosage and administration details:

NaCl 0,9% with an equal volume nebulized 3 times per day for 5 days.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Iloprost arm | Control arm |
|---|--------------|-------------|
| Started   | 72           | 72          |
| Completed   | 72           | 72          |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of patients enrolled was 150. The number of subjects analyzed was 144 (Iloprost n=72, Control n=72). There were 6 drop-out patients.

## Baseline characteristics

## End points

### End points reporting groups

|  |              |
|--|--------------|
| Reporting group title  | Iloprost arm |
| Reporting group description:                                     |              |
| Investigational arm who received Iloprost Trometamol (Ventavis). |              |
| Reporting group title  | Control arm  |
| Reporting group description:                                     |              |
| Placebo arm (NaCl)   |              |

### Primary: Difference in Improvement of oxygenation (paO<sub>2</sub>/FiO<sub>2</sub> ratio) Iloprost vs NaCl

|                        |  |
|------------------------|--|
| End point title        | Difference in Improvement of oxygenation (paO <sub>2</sub> /FiO <sub>2</sub> ratio) Iloprost vs NaCl <sup>[1]</sup>  |
| End point description: | The primary outcome was the PaO <sub>2</sub> /FiO <sub>2</sub> ratio on Day 5 following treatment with the study drug. The PaO <sub>2</sub> /FiO <sub>2</sub> ratio at baseline was not significantly different between groups. Following treatment with Iloprost, the PaO <sub>2</sub> /FiO <sub>2</sub> ratio showed a tendency to improve when considering all patients included in the trial. The primary group showed a strong tendency toward improvement (difference in improvement Iloprost vs. comparator NaCl groups of 19.5mmHg, baseline adjusted 20.1 mmHg, p=0.177, 95% CI (-9.1)-(+49.4) following Iloprost inhalation. |
| End point type         | Primary  |
| End point timeframe:   | 5 days   |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Attached can be found a chart with further statistical analysis and the secondary endpoints.

| End point values                     | Iloprost arm    | Control arm     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 72              | 72              |  |  |
| Units: mmHg                          |                 |                 |  |  |
| arithmetic mean (standard deviation) | 104.7 (± 90.5)  | 85.0 (± 84.3)   |  |  |

|                                   |                             |
|-----------------------------------|-----------------------------|
| <b>Attachments (see zip file)</b> | Clinical Outcomes Thilo.PNG |
|-----------------------------------|-----------------------------|

### Statistical analyses

No statistical analyses for this end point

## Adverse events

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

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Timeframe for reporting adverse events:

the period of observation for collection of adverse events extends from the time of the first dose until the visit at day 28.

Adverse event reporting additional description:

All adverse events from CTCAE grade 3 (see Chapter 10.2.2) have to be reported (whether serious or non-serious) and must be documented on the "adverse event" page of the eCRFs.

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|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

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### Dictionary used

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|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

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|                    |   |
|--------------------|---|
| Dictionary version | 5 |
|--------------------|---|

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

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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: Adverse Events Table can be found attached

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                       |
|------------------|---------------------------------|
| 16 December 2020 | Latest Protocol Version Nr. 6.0 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported