Clinical trial results:
Therapeutic Iloprost for the treatment of Acute Respiratory Distress Syndrome (ARDS) (the ThIlo-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	ThIlo

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 paO2/FiO2 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
Arm title	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.

Arm title	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.

Number of subjects in period 1[1]	Iloprost arm	Control arm
Started	72	72
Completed	72	72

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 (paO2/FiO2 ratio) Iloprost vs NaCl

End point title	Difference in Improvement of oxygenation (paO2/FiO2 ratio) Iloprost vs NaCl[1]

End point description:

The primary outcome was the PaO2/FiO2 ratio on Day 5 following treatment with the study drug. The PaO2/FiO2 ratio at baseline was not significantly different between groups. Following treatment with Iloprost, the PaO2/FiO2 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)		

Attachments (see zip file)	Clinical Outcomes Thilo.PNG

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
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.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5

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

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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported