# The TRISTARDS trial - ThRombolysIS Therapy for ARDS
# A Phase IIb/III operationally seamless, open-label, randomised, sequential, parallel-group adaptive study to evaluate the efficacy and safety of daily intravenous alteplase treatment given up to 5 days on top of standard of care (SOC) compared with SOC alone, in patients with acute respiratory distress syndrome (ARDS) triggered by COVID-19.

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Last updated: 08-04-2024

Main objective is to evaluate the efficacy and safety of two (Part 1) different dosing regimen and of one dosing regimen (Part 2) of intravenous alteplase given for up to 5 days on top of standard of care (SOC) compared with SOC alone in ARDS...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Viral infectious disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON52082

**Source**
ToetsingOnline

**Brief title**
TRISTARDS Trial

## Condition

- Viral infectious disorders
- Pulmonary vascular disorders

**Synonym**
Acute lung injury, shocklung

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Boehringer Ingelheim
**Source(s) of monetary or material Support:** Boehringer Ingelheim BV

## Intervention

**Keyword:** Acute respiratory distress syndrome (ARDS), Alteplase, COVID-19, efficacy and safety

## Outcome measures

### Primary outcome

Time to clinical improvement or hospital discharge up to Day 28, defined as the

time from randomisation to either an improvement of two points on the 11-point

WHO Clinical Progression Scale or discharge from the hospital, whichever comes

first.

### Secondary outcome

- All cause mortality at Day 28

- Number of ventilator-free days from start of treatment to Day 28

- Improvement of Sequential (sepsis-related) Organ Failure Assessment (SOFA)

score by >=2 points from baseline to end of Day 6

- Major bleeding events (MBE) (according to International Society on Thrombosis

and Haemostasis [ISTH] definition until Day 6

- Daily average PaO2/FiO2 ratio (or inferred PaO2/FiO2 ratio from SpO2) change

from baseline to Day 6

- All-cause mortality or on mechanical ventilation at Day 28

- Treatment failure defined as all cause mortality or mechanical ventilation at

Day 28

- Number of oxygen-free days up to Day 28

- Length of hospital stay up to Day 28

- PaO2/FiO2 ratio (or inferred PaO2/FiO2 ratio from SpO2) change from baseline

to Day 6

# Study description

**Background summary**

The number of COVID-19 infections is still rising worldwide.

In a significant proportion of the population, particularly the elderly, COVID-19 results in ARDS. Experience suggests that 5 to 16% of patients hospitalised with COVID-19 will undergo prolonged intensive care and 50 to 70% thereof require mechanical ventilation. The mortality rate is 25 to 60% in severely affected patients with ARDS with the current standard of care.

COVID-19 and other infections are associated with ARDS. The exact mechanism contributing to a rapid lung injury in patients with ARDS is not fully understood, but diffuse alveolar damage typically marks the onset of ARDS. This leads to the formation of microthrombi in the lungs and further compromising gas exchange.

ARDS has no effective specific treatment besides supportive care.

As an established thrombolytic therapy, alteplase may have a role in targeting the coagulation and fibrinolytic systems to improve the treatment and possibly outcome of ARDS.

See protocol section 1.1.

## Study objective

Main objective is to evaluate the efficacy and safety of two (Part 1) different dosing regimen and of one dosing regimen (Part 2) of intravenous alteplase given for up to 5 days on top of standard of care (SOC) compared with SOC alone in ARDS associated with COVID-19. SOC includes supportive measures, such as the use of non-invasive or invasive ventilation, haemodynamic support, if needed, sedation, as well as medical therapies commonly used in patients suffering from ARDS or its complications. SOC follows the standard therapies established locally.

See protocol section 2.1.1.

## Study design

This is an open-label operationally seamless Phase IIb/III randomised, sequential, parallel-group adaptive clinical trial in patients experiencing ARDS triggered by COVID-19, comparing daily intravenous infusion of alteplase, up to a maximum treatment duration of 5 days on top of SOC, versus SOC alone.

## Intervention

Treatment with Alteplase IV.

Part 1 of the trial (1:1:1 ratio):
Dosing regimen A (based on your body weight):
• Initial dose of alteplase will be (0,3 mg/kg body weight) given intravenously over a period of 2 hours.
• Followed by daily infusion of alteplase (0,02 mg/kg/hour) given over a period of 12 hours from day 1 up to and including day 5.
• Optionally, one additional dose of alteplase (0,3 mg/kg body weight) can be given to you intravenously over a period of 2 hours on Days 2 to 5 if the trial doctor determines the need, based on your condition.
OR
Dosing regimen B (based on your body weight):
• Initial dose of alteplase will be (0,6 mg/kg body weight) given intravenously over a period of 2 hours.
• Followed by daily infusion of alteplase /0,04 mg/kg/hour) given over a period of 12 hours from day 1up to and including day 5.
• Optionally, one additional dose of alteplase (0,6 mg/kg body weight) can be given to you intravenously over a period of 2 hours on Days 2 to 5 if the trial doctor determines the need, based on your condition.
OR
3. Standard treatment for your condition (Standard of Care)

Part 2 of the trial:
One dosing regimen will be carried forward based on results from Part 1 and recommendation by the DMC for Part 2.
Dosing regiment for Part 2:
• Initial dose of alteplase will be (0.6mg/kg body weight) given intravenously over a period of 2 hours.
• Followed by daily infusion of alteplase (0,04 mg/kg/hour) given over a period of 12hours from day 1 up to and including day 5*
• Optionally, one additional i.v. infusion of 0.6 mg/kg over 2 hours can be given once on Days 2 to 5 in case of clinical worsening (as per investigator judgement).

*Exception: Treatment period can be exceeded beyond Day 5, in case of unavoidable interruptions of the treatment. See protocol 1.4.

**Study burden and risks**

Burden:
The study will last approximately 3 months in total. If patients are dismissed from the hospital before the end of the study, they will have to visit the hospital for a few more visits.
During the visits, the following shall be carried out:
Physical examination: 3x
ECG: 7x
Vital signs: 8x
Blood gas or saturation measurement: 9x
Blood collection: 8x
COVID-19 test: 2x
Pregnancy test: 2x
Additional (optional) blood sampling for PK (3 tubes): 2x

Risks:
Risks of adverse reactions or allergic reaction to study medication.
Risks of adverse reactions to study procedures, such as bruising after venapunction.

# Contacts

**Public**
Boehringer Ingelheim

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NL

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NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Age >= 18 years (or above legal age)
2. ARDS with PaO2*/FiO2 ratio >100 and <=300 , either on non-invasive ventilator support, OR on mechanical ventilation (<48 hours since intubation),
- with bilateral opacities in chest X-ray or CT scan
- with respiratory failure
*or estimation of PaO2/FiO2 from pulse oximetry (SpO2/FiO2)
3. SARS-CoV-2 positive (laboratory-confirmed RT-PCR test)
4. Fibrinogen level >= lower limit of normal
5. D-Dimer >= upper limit of normal (ULN) according to local laboratory
6. Signed and dated written informed consent in accordance with ICH GCP and local legislation prior to admission to the trial.

See protocol section 3.3.2.

## Exclusion criteria

1. Massive confirmed pulmonary embolism (PE) with haemodynamic instability at trial entry, or any (suspected or confirmed) PE that is expected to require

therapeutic dosages of anticoagulants during the treatment period.
2. Indication for therapeutic dosages of anticoagulants at trial entry.
3. Patients on mechanical ventilation for longer than 48 hours
4. Chronic pulmonary disease i.e. with known forced expiratory volume in 1 second (FEV1) <50% requiring home oxygen, or oral steroid therapy or hospitalisation for exacerbation within 12 months, or significant chronic pulmonary disease in the Investigator*s opinion, or primary pulmonary arterial hypertension
5. Has a Do-Not-Intubate (DNI) or Do-Not-Resuscitate (DNR) order
6. In the opinion of the investigator, is not expected to survive for >48 hours after screening.
7. Planned interventions during the first 5 days after randomization, such as surgery, insertion of central catheter or arterial line, drains, etc.
8. Patients with known hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients
9. Significant bleeding disorder at present or within the past 3 months, known haemorrhagic diathesis
10. Patients receiving effective oral anticoagulant treatment, e.g. vitamin K antagonists with INR >1.3, or any direct oral anticoagulant within the past 48 hours
11. Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
12. History or evidence or suspicion of intracranial haemorrhage including sub-arachnoid haemorrhage
13. Severe uncontrolled arterial hypertension (according to the investigator`s judgement)
14. Major surgery or significant trauma in the past 10 days, recent trauma to head or cranium
15. Cardiac arrest and/or cardiopulmonary resuscitation during the current hospital stay
16. Obstetrical delivery within the past 10 days
17. Severe hepatic dysfunction i.e. Child-Pugh B and C, including biopsy confirmed hepatic cirrhosis, portal hypertension, hepatic encephalopathy, or active hepatitis
18. Bacterial endocarditis, pericarditis
19. Acute pancreatitis
20. Documented ulcerative gastro-intestinal disease during the last 3 months
21. Severe heart failure (New York Heart Association Class IV)
22. Arterial aneurysms, arterial/venous malformations
23. Malignancy (Stage IV) with increased bleeding risk
24. Haemorrhagic stroke or stroke of unknown origin at any time
25. Ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months

Further criteria apply, see protocol section 3.3.3.

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 08-03-2021 |
| Enrollment: | 5 |
| Type: | Actual |

## Medical products/devices used

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| Product type: | Medicine |
| Brand name: | Actilyse |
| Generic name: | Alteplase |
| Registration: | Yes - NL outside intended use |

# Ethics review

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| Approved WMO Date: | 17-11-2020 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 20-01-2021 |
| Application type: | First submission |

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| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 16-02-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 25-02-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 16-03-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 18-03-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 14-10-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 19-11-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 10-03-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

Approved WMO

| | |
|---|---|
| Date: | 15-03-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 01-04-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 15-04-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 21-07-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 22-07-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
| --- | --- |
| EudraCT | EUCTR2020-002913-16-NL |
| ClinicalTrials.gov | NCT04640194 |
| CCMO | NL75709.100.20 |