Clinical trial results:
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

Summary

EudraCT number	2020-002913-16
Trial protocol	BE DE AT PT NL FR DK IT PL RO ES
Global end of trial date	25 July 2022

Results information

Result version number	v1 (current)
This version publication date	09 August 2023
First version publication date	09 August 2023

Trial information

Trial identification

Sponsor protocol code	0135-0347

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04640194
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com

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	16 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2022
Global end of trial reached?	Yes
Global end of trial date	25 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of intravenous alteplase in ARDS triggered by COVID-19.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all subjects as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2021
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	Austria: 10
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Mexico: 2
Worldwide total number of subjects	104
EEA total number of subjects	95

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)	59
From 65 to 84 years	42
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

A Phase IIb/III randomised, controlled, open-label, sequential, parallel-group, operationally seamless adaptive study with two parts.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

Period 1

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

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Alteplase low dose

Arm description:

0.3 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.02 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.3 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.

Arm type	Experimental
Investigational medicinal product name	Alteplase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.3 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.02 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.3 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.

Arm title	Part 1: Alteplase high dose

Arm description:

0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.

Arm type	Experimental
Investigational medicinal product name	Alteplase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of

clinical worsening, per investigator judgement.

Arm title	Part 1: Standard of Care

Arm description:

Standard of Care included best possible treatment regimen established locally and was in line with current guidelines for Acute respiratory distress syndrome treatment.

Arm type	Standard of Care

No investigational medicinal product assigned in this arm

Arm title	Part 2: Alteplase high dose - NIV patients

Arm description:

Non-invasive mechanical ventilation (NIV) patients received 0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement. Non-invasive mechanical ventilation (NIV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 6.

Arm type	Experimental
Investigational medicinal product name	Alteplase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.

Arm title	Part 2: Standard of Care - NIV patients

Arm description:

Non-invasive mechanical ventilation (NIV) patients received Standard of Care, which included best possible treatment regimen established locally and were in line with current guidelines for Acute respiratory distress syndrome treatment. Non-invasive mechanical ventilation (NIV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 6.

Arm type	Standard of Care

No investigational medicinal product assigned in this arm

Arm title	Part 2: Alteplase high dose - IMV patients

Arm description:

Invasive mechanical ventilation (IMV) patients received 0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement. Invasive mechanical ventilation (IMV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 7, 8 or 9.

Arm type	Experimental
Investigational medicinal product name	Alteplase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One

optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.

Arm title	Part 2: Standard of Care - IMV patients
Arm description:	
invasive mechanical ventilation (IMV) patients received Standard of Care, which included best possible treatment regimen established locally and was in line with current guidelines for Acute respiratory distress syndrome treatment. Invasive mechanical ventilation (IMV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 7, 8 or 9.	
Arm type	Standard of Care
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care
Started	20	20	22
Completed	17	12	22
Not completed	3	8	0
pO2/FIO2 ratio too high	-	-	-
Adverse event, non-fatal	3	7	-
Transferred from IC Unit to Hospital Ward	-	1	-
mild bleeding	-	-	-
fibrinogen level too low	-	-	-

Number of subjects in period 1	Part 2: Alteplase high dose - NIV patients	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients
Started	17	8	12
Completed	9	8	8
Not completed	8	0	4
pO2/FIO2 ratio too high	1	-	-
Adverse event, non-fatal	5	-	4
Transferred from IC Unit to Hospital Ward	-	-	-
mild bleeding	1	-	-
fibrinogen level too low	1	-	-

Number of subjects in period 1	Part 2: Standard of Care - IMV patients
Started	5
Completed	5
Not completed	0
pO2/FIO2 ratio too high	-
Adverse event, non-fatal	-
Transferred from IC Unit to Hospital Ward	-

mild bleeding	-
fibrinogen level too low	-

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Alteplase low dose
Reporting group description:	
0.3 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.02 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.3 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.	
Reporting group title	Part 1: Alteplase high dose
Reporting group description:	
0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.	
Reporting group title	Part 1: Standard of Care
Reporting group description:	
Standard of Care included best possible treatment regimen established locally and was in line with current guidelines for Acute respiratory distress syndrome treatment.	
Reporting group title	Part 2: Alteplase high dose - NIV patients
Reporting group description:	
Non-invasive mechanical ventilation (NIV) patients received 0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement. Non-invasive mechanical ventilation (NIV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 6.	
Reporting group title	Part 2: Standard of Care - NIV patients
Reporting group description:	
Non-invasive mechanical ventilation (NIV) patients received Standard of Care, which included best possible treatment regimen established locally and were in line with current guidelines for Acute respiratory distress syndrome treatment. Non-invasive mechanical ventilation (NIV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 6.	
Reporting group title	Part 2: Alteplase high dose - IMV patients
Reporting group description:	
Invasive mechanical ventilation (IMV) patients received 0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement. Invasive mechanical ventilation (IMV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 7, 8 or 9.	
Reporting group title	Part 2: Standard of Care - IMV patients
Reporting group description:	
invasive mechanical ventilation (IMV) patients received Standard of Care, which included best possible treatment regimen established locally and was in line with current guidelines for Acute respiratory distress syndrome treatment. Invasive mechanical ventilation (IMV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 7, 8 or 9.	

Reporting group values	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care
Number of subjects	20	20	22
Age categorical			
treated set (TS) included all patients who were randomised and for the alteplase groups, treated with at least one dose.			
Units: Subjects			
In utero	0	0	0

Preterm newborn infants (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)	9	13	13
From 65-84 years	11	7	9
85 years and over	0	0	0
Age Continuous			
The Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint of interest.			
Units: years			
arithmetic mean	61.0	61.6	60.3
standard deviation	± 12.0	± 9.8	± 13.0
Sex: Female, Male			
The Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint of interest.			
Units: Participants			
Female	10	3	9
Male	10	17	13
Race/Ethnicity, Customized			
The Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint of interest.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
White	13	13	14
Native Hawaiian or Other Pacific Islander & White	0	0	1
American Indian or Alaska Native & White	0	0	0
Missing	7	7	5
World Health Organization (WHO) Clinical Progression Scale			
WHO Clinical Progression Scale ranges from 0 to 10, low score indicates better outcome. 0=Uninfected; no viral RNA detected 1=Asymptomatic; viral RNA detected 2=Symptomatic; independent 3=Symptomatic; assistance needed 4=Hospitalised; no oxygen therapy 5=Hospitalised; oxygen by mask or nasal prongs 6=Hospitalised; oxygen by NIV or high flow 7=Intubation and mechanical ventilation, PaO2/FiO2=150 or SpO2/FiO2=200 8=Mechanical ventilation PaO2/FiO2 <150 (SpO2/FiO2 <200) or vasopressors 9=Mechanical ventilation PaO2/FiO2 <150 and vasopressors, dialysis, or ECMO 10=Dead. FAS.			
Units: Subjects			
WHO scale 0	0	0	0
WHO scale 1	0	0	0
WHO scale 2	0	0	0
WHO scale 3	0	0	0
WHO scale 4	0	0	0
WHO scale 5	0	0	0
WHO scale 6	16	16	16
WHO scale 7	1	1	3

WHO scale 8	2	0	1
WHO scale 9	1	3	2
WHO scale 10	0	0	0

Reporting group values	Part 2: Alteplase high dose - NIV patients	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients
Number of subjects	17	8	12
Age categorical			
treated set (TS) included all patients who were randomised and for the alteplase groups, treated with at least one dose.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (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)	9	7	6
From 65-84 years	6	0	6
85 years and over	2	1	0
Age Continuous			
The Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint of interest.			
Units: years			
arithmetic mean	63.4	60.5	59.7
standard deviation	± 11.5	± 10.9	± 11.1
Sex: Female, Male			
The Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint of interest.			
Units: Participants			
Female	3	5	1
Male	14	3	11
Race/Ethnicity, Customized			
The Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint of interest.			
Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	10	3	7
Native Hawaiian or Other Pacific Islander & White	0	0	0
American Indian or Alaska Native & White	1	0	0
Missing	5	5	5
World Health Organization (WHO) Clinical Progression Scale			
WHO Clinical Progression Scale ranges from 0 to 10, low score indicates better outcome. 0=Uninfected; no viral RNA detected 1=Asymptomatic; viral RNA detected 2=Symptomatic; independent 3=Symptomatic; assistance needed 4=Hospitalised; no oxygen therapy 5=Hospitalised; oxygen by mask or nasal prongs 6=Hospitalised; oxygen by NIV or high flow 7=Intubation and mechanical ventilation, PaO2/FiO2=150 or SpO2/FiO2=200 8=Mechanical ventilation PaO2/FiO2 <150 (SpO2/FiO2			

<200) or vasopressors 9=Mechanical ventilation PaO2/FiO2 <150 and vasopressors, dialysis, or ECMO 10=Dead. FAS.			
Units: Subjects			
WHO scale 0	0	0	0
WHO scale 1	0	0	0
WHO scale 2	0	0	0
WHO scale 3	0	0	0
WHO scale 4	0	0	0
WHO scale 5	0	0	0
WHO scale 6	17	8	0
WHO scale 7	0	0	1
WHO scale 8	0	0	8
WHO scale 9	0	0	3
WHO scale 10	0	0	0

Reporting group values	Part 2: Standard of Care - IMV patients	Total	
Number of subjects	5	104	
Age categorical			
treated set (TS) included all patients who were randomised and for the alteplase groups, treated with at least one dose.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	59	
From 65-84 years	3	42	
85 years and over	0	3	
Age Continuous			
The Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint of interest.			
Units: years			
arithmetic mean	67.6		
standard deviation	± 10.5	-	
Sex: Female, Male			
The Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint of interest.			
Units: Participants			
Female	1	32	
Male	4	72	
Race/Ethnicity, Customized			
The Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint of interest.			
Units: Subjects			
American Indian or Alaska Native	0	1	
Asian	0	0	
Black or African American	0	2	
Native Hawaiian or Other Pacific Islander	0	0	

White	1	61	
Native Hawaiian or Other Pacific Islander & White	0	1	
American Indian or Alaska Native & White	0	1	
Missing	4	38	
World Health Organization (WHO) Clinical Progression Scale			
WHO Clinical Progression Scale ranges from 0 to 10, low score indicates better outcome. 0=Uninfected; no viral RNA detected 1=Asymptomatic; viral RNA detected 2=Symptomatic; independent 3=Symptomatic; assistance needed 4=Hospitalised; no oxygen therapy 5=Hospitalised; oxygen by mask or nasal prongs 6=Hospitalised; oxygen by NIV or high flow 7=Intubation and mechanical ventilation, PaO2/FiO2=150 or SpO2/FiO2=200 8=Mechanical ventilation PaO2/FiO2 <150 (SpO2/FiO2 <200) or vasopressors 9=Mechanical ventilation PaO2/FiO2 <150 and vasopressors, dialysis, or ECMO 10=Dead. FAS.			
Units: Subjects			
WHO scale 0	0	0	
WHO scale 1	0	0	
WHO scale 2	0	0	
WHO scale 3	0	0	
WHO scale 4	0	0	
WHO scale 5	0	0	
WHO scale 6	0	73	
WHO scale 7	3	9	
WHO scale 8	0	11	
WHO scale 9	2	11	
WHO scale 10	0	0	

End points

End points reporting groups

Reporting group title	Part 1: Alteplase low dose

Reporting group description:

0.3 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.02 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.3 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.

Reporting group title	Part 1: Alteplase high dose

Reporting group description:

0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.

Reporting group title	Part 1: Standard of Care

Reporting group description:

Standard of Care included best possible treatment regimen established locally and was in line with current guidelines for Acute respiratory distress syndrome treatment.

Reporting group title	Part 2: Alteplase high dose - NIV patients

Reporting group description:

Non-invasive mechanical ventilation (NIV) patients received 0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement. Non-invasive mechanical ventilation (NIV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 6.

Reporting group title	Part 2: Standard of Care - NIV patients

Reporting group description:

Non-invasive mechanical ventilation (NIV) patients received Standard of Care, which included best possible treatment regimen established locally and were in line with current guidelines for Acute respiratory distress syndrome treatment. Non-invasive mechanical ventilation (NIV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 6.

Reporting group title	Part 2: Alteplase high dose - IMV patients

Reporting group description:

Invasive mechanical ventilation (IMV) patients received 0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement. Invasive mechanical ventilation (IMV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 7, 8 or 9.

Reporting group title	Part 2: Standard of Care - IMV patients

Reporting group description:

invasive mechanical ventilation (IMV) patients received Standard of Care, which included best possible treatment regimen established locally and was in line with current guidelines for Acute respiratory distress syndrome treatment. Invasive mechanical ventilation (IMV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 7, 8 or 9.

Primary: Time to clinical improvement or hospital discharge up to Day 28

End point title	Time to clinical improvement or hospital discharge up to Day 28

End point description:

From randomisation to either an improvement of 2 points on the 11-point World Health Organization (WHO) Clinical Progression Scale (from 0 to 10, a low score indicates a better outcome) or discharge from the hospital, whichever comes first.
0=Uninfected; no viral RNA detected

1=Asymptomatic; viral RNA detected
2=Symptomatic; independent
3=Symptomatic; assistance needed
4=Hospitalised; no oxygen therapy
5=Hospitalised; oxygen by mask or nasal prongs
6=Hospitalised; oxygen by NIV or high flow
7=Intubation and mechanical ventilation, PaO2/FiO2=150 or SpO2/FiO2=200
8=Mechanical ventilation PaO2/FiO2<150 (SpO2/FiO2<200) or vasopressors
9=Mechanical ventilation PaO2/FiO2<150 and vasopressors, dialysis, or ECMO
10=Dead
Patients that not met the endpoint were censored (Day 28) if they died prior to Day 28. Patients receiving bail out therapy without having first met the endpoint, were censored on the day of bail-out (hypothetical estimand).
FAS.

End point type	Primary

End point timeframe:

Up to 28 days.

End point values	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care	Part 2: Alteplase high dose - NIV patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20[1]	20[2]	22[3]	17[4]
Units: days				
median (confidence interval 95%)	9999 (14.0 to 9999)	19.0 (9.0 to 9999)	9999 (17.0 to 9999)	22.0 (7.0 to 9999)

Notes:

[1] - 9999 = Median and Upper limit not achieved due to insufficient numbers of participants with events.
[2] - 9999 = Upper limit was not achieved, due to insufficient numbers of participants with events.

[3] - 9999 = Median and Upper limit not achieved due to insufficient numbers of participants with events.
[4] - 9999 = Upper limit was not achieved, due to insufficient numbers of participants with events.

End point values	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients	Part 2: Standard of Care - IMV patients	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8[5]	12[6]	5[7]	
Units: days				
median (confidence interval 95%)	9999 (8.0 to 9999)	25.5 (13.0 to 9999)	9999 (4.0 to 9999)	

Notes:

[5] - 9999 = Median and Upper limit not achieved due to insufficient numbers of participants with events.
[6] - 9999 = Upper limit was not achieved, due to insufficient numbers of participants with events.

[7] - 9999 = Median and Upper limit not achieved due to insufficient numbers of participants with events.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Unadjusted Hazard Ratio: Cox proportional hazard model containing fixed effect for treatment. The confidence intervals was determined using the Wald method to determine the variance.

Comparison groups	Part 1: Alteplase low dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	2.61

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Unadjusted Hazard Ratio: Cox proportional hazard model containing fixed effect for treatment. The confidence intervals was determined using the Wald method to determine the variance.

Comparison groups	Part 1: Alteplase high dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	4.15

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Adjusted Hazard Ratio: Cox proportional hazard model containing fixed effect for treatment, ventilation status at baseline and age. The confidence intervals was determined using the Wald method to determine the variance.

Comparison groups	Part 1: Alteplase low dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	3.27

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Adjusted Hazard Ratio: Cox proportional hazard model containing fixed effect for treatment, ventilation status at baseline and age. The confidence intervals was determined using the Wald method to determine the variance.

Comparison groups	Part 1: Alteplase high dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	5.01

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

Unadjusted Hazard Ratio: Cox proportional hazard model containing fixed effect for treatment. The confidence intervals was determined using the Wald method to determine the variance.

Comparison groups	Part 2: Alteplase high dose - NIV patients v Part 2: Standard of Care - NIV patients
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	3.66

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

Adjusted Hazard Ratio: Cox proportional hazard model containing fixed effect for treatment, ventilation status at baseline and age. The confidence intervals was determined using the Wald method to determine the variance.

Comparison groups	Part 2: Alteplase high dose - NIV patients v Part 2: Standard of Care - NIV patients
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	4.22

Secondary: Number of subjects with major bleeding events (MBE) at Day 6

End point title	Number of subjects with major bleeding events (MBE) at Day 6

End point description:

Number of subjects with major bleeding events (MBE). Major bleeding events (MBE) according to International Society on Thrombosis and Haemostasis [ISTH] definition until Day 6. Definition of a major bleed:

•Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,

and/or

•Bleeding associated with a reduction in hemoglobin of at least 2 gram/deciliter (1.24 millimole/Liter), or leading to transfusion of two or more units of blood or packed cells

and/or

•Fatal bleed

The Treated Set (TS) consisted of all patients who were randomised and, for patients in the alteplase groups, treated with at least one dose of trial drug.

End point type	Secondary

End point timeframe:

From start of treatment (Alteplase) or randomisation (SOC) (day 1) till Day 6, up to 6 days.

End point values	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care	Part 2: Alteplase high dose - NIV patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	22	17
Units: Participants	1	4	0	2

End point values	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients	Part 2: Standard of Care - IMV patients	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	12	5	
Units: Participants	0	2	0	

Statistical analyses

Statistical analysis title	Statistical analysis 7
Statistical analysis description: Chan and Zhang exact confidence interval.	
Comparison groups	Part 1: Alteplase low dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.892
upper limit	24.8734

Statistical analysis title	Statistical analysis 9
Statistical analysis description: Chan and Zhang exact confidence interval.	
Comparison groups	Part 2: Alteplase high dose - NIV patients v Part 2: Standard of Care - NIV patients
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	11.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.127
upper limit	36.9012

Statistical analysis title	Statistical analysis 8
Statistical analysis description: Chan and Zhang exact confidence interval.	
Comparison groups	Part 1: Alteplase high dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3075
upper limit	43.6615

Secondary: All cause mortality at Day 28

End point title	All cause mortality at Day 28

End point description:

All cause mortality at Day 28. If it is unknown whether the patient was dead at end of Day 28, then it will be assumed that the patient did not die up to Day 28, regardless of the reason. This unfavorable endpoint is met if:
- the last known status of the patient is 10 on the WHO clinical progression scale by the end of Day 28, or
- vital status is dead within 28 days

Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint.

End point type	Secondary

End point timeframe:

Up to 28 days.

End point values	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care	Part 2: Alteplase high dose - NIV patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	22	17
Units: Participants	2	3	6	1

End point values	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients	Part 2: Standard of Care - IMV patients	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	12	5	
Units: Participants	2	2	2	

Statistical analyses

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

Adjusted risk difference and 95% confidence interval is based upon average marginal effect Delta method, adjusting for baseline ventilation status, age and treatment.

Comparison groups	Part 1: Alteplase low dose v Part 1: Standard of Care

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	-16.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.6
upper limit	5.5

Statistical analysis title	Statistical analysis 11
Statistical analysis description:	
Adjusted risk difference and 95% confidence interval is based upon average marginal effect Delta method, adjusting for baseline ventilation status, age and treatment.	
Comparison groups	Part 1: Alteplase high dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	-11.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.1
upper limit	11.6

Statistical analysis title	Statistical analysis 12
Statistical analysis description:	
Unadjusted risk difference and 95% CI is based upon average marginal effect Delta method, adjusting for treatment.	
Comparison groups	Part 2: Alteplase high dose - NIV patients v Part 2: Standard of Care - NIV patients
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2419
Method	The delta method and average marginal.
Parameter estimate	Risk difference (RD)
Point estimate	-19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.1
upper limit	12.9

Secondary: Treatment failure at Day 28

End point title	Treatment failure at Day 28

End point description:

Treatment failure defined as all cause mortality or mechanical ventilation at Day 28.

Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint.

End point type	Secondary

End point timeframe:

Up to 28 days.

End point values	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care	Part 2: Alteplase high dose - NIV patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	22	17
Units: Participants	8	8	11	6

End point values	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients	Part 2: Standard of Care - IMV patients	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	12	5	
Units: Participants	3	5	3	

Statistical analyses

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

Adjusted risk difference and 95% confidence interval is based upon average marginal effect Delta method, adjusting for baseline ventilation status, age and treatment.

Comparison groups	Part 1: Alteplase low dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	-9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.1
upper limit	19.1

Statistical analysis title	Statistical analysis 14

Statistical analysis description:

Adjusted risk difference and 95% CI is based upon average marginal effect Delta method, adjusting for baseline D-dimer status, age, days of NIV support and treatment.

Comparison groups	Part 2: Alteplase high dose - NIV patients v Part 2: Standard of Care - NIV patients
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2523
Method	The delta method and average marginal.
Parameter estimate	Risk difference (RD)
Point estimate	14.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	39.3

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

Adjusted risk difference and 95% confidence interval is based upon average marginal effect Delta method, adjusting for baseline ventilation status, age and treatment.

Comparison groups	Part 1: Alteplase high dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.2
upper limit	19

Secondary: Number of ventilator-free days at Day 28

End point title	Number of ventilator-free days at Day 28[8]

End point description:

Number of ventilator-free days (VFDs) from start of treatment to Day 28. ‘Ventilator’ is defined as

'assisted breathing' but it refers to mechanical invasive ventilation. The number of VFDs starts from when the patient has a 'lasting' value on the WHO clinical progression scale of ≤ 6, and ends on Day 28. A lasting value of ≤ 6 means that the value cannot exceed 6 at a later timepoint. If the patient is liberated from the ventilator on Day x, then the number of VFDs is 28-x. If a patient has withdrawn consent prior to day 28 then he will have a missing value for VFD. In any case, if the status of the patient at Day 28 is death, as determined from the vital status page then the VFD=0.

Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint. The endpoint was only planned for subjects in Part 1.

End point type	Secondary

End point timeframe:

Up to 28 days.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint only analyzed part 1 subjects.

End point values	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	22	
Units: Days				
arithmetic mean (standard error)	10.6 (± 2.9)	11.8 (± 2.9)	7.5 (± 2.7)	

Statistical analyses

Statistical analysis title	Statistical analysis 15

Statistical analysis description:

Parameters included in model: treatment,ventilation status at baseline, and age.

Comparison groups	Part 1: Alteplase low dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	10.6
Variability estimate	Standard error of the mean
Dispersion value	3.7

Statistical analysis title	Statistical analysis 16

Statistical analysis description:

Parameters included in model: treatment,ventilation status at baseline, and age.

Comparison groups	Part 1: Alteplase high dose v Part 1: Standard of Care

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Median difference (final values)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	11.8
Variability estimate	Standard error of the mean
Dispersion value	3.7

Secondary: Daily average PaO2/FiO2 ratio change from baseline to Day 6

End point title	Daily average PaO2/FiO2 ratio change from baseline to Day 6[9]

End point description:

Daily average PaO2/FiO2 ratio (or inferred PaO2/FiO2 ratio from SpO2) change from baseline to Day 6. This was measured 3-times daily. All available values of these days, regardless of the position of the patient when being measured, were averaged to determine the daily average PaO2/FiO2 ratio for that patient. The higher the value the better the health status of the patient. If patient was still in hospital during day 6 then the day 6 daily average value was used, if available. If the patient was discharged from hospital prior to day 6 then the daily average at the time of hospital discharge was used as a surrogate for day 6, if available. If the patient died prior to day 6 then there was no imputation but handled as failure in the determination of the difference in medians and CI. Based upon this, the change from baseline for each patient was calculated.
FAS. Only subjects with non-missing endpoint data were included. The endpoint was only planned for subjects in Part 1.

End point type	Secondary

End point timeframe:

Up to 6 days.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint only analyzed part 1 subjects.

End point values	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	19	22	
Units: PaO2/FiO2 ratio				
median (inter-quartile range (Q1-Q3))	32.2 (-24.0 to 56.2)	58.5 (10.1 to 150.4)	7.5 (-14.7 to 33.5)	

Statistical analyses

Statistical analysis title	Statistical analysis 19

Statistical analysis description:

Based upon Hedges-Lehmann estimator handling deaths as failure and Wilcoxon rank sum test methodology.

Comparison groups	Part 1: Alteplase low dose v Part 1: Standard of Care

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Median difference (net)
Point estimate	17.193
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.45
upper limit	52.33

Statistical analysis title	Statistical analysis 20

Statistical analysis description:

Based upon Hedges-Lehmann estimator handling deaths as failure and Wilcoxon rank sum test methodology.

Comparison groups	Part 1: Alteplase high dose v Part 1: Standard of Care
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Median difference (final values)
Point estimate	54.436
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	110.36

Secondary: Number of subjects with improvement of Sequential (sepsis-related) Organ Failure Assessment (SOFA) score by ≥2 points at day 6

End point title	Number of subjects with improvement of Sequential (sepsis-related) Organ Failure Assessment (SOFA) score by ≥2 points at day 6[10]

End point description:

Number of subjects with improvement of Sequential (sepsis-related) Organ Failure Assessment (SOFA) score by ≥2 points from baseline to end of Day 6. The Sequential Organ Failure Assessment (SOFA) scores six variables: respiratory, coagulation, liver, Cardiovascular, central nervous system and renal. Each variable is score from 0 (best outcome) to 4 (worst outcome) with a total score calculated as the sum of all six variables ranging from 0 (best outcome) to 24 (worst outcome).

Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint. The endpoint was only planned for subjects in Part 1.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Day 6 of treatment

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint only analyzed part 1 subjects.

End point values	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	22	
Units: Participants	4	2	6	

Statistical analyses

Statistical analysis title	Statistical analysis 18
Statistical analysis description:	
Adjusted risk difference and 95% confidence interval is based upon average marginal effect Delta method, adjusting for baseline ventilation status, age and treatment.	
Comparison groups	Part 1: Alteplase high dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	-15.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.8
upper limit	6.3

Statistical analysis title	Statistical analysis 17
Statistical analysis description:	
Adjusted risk difference and 95% confidence interval is based upon average marginal effect Delta method, adjusting for baseline ventilation status, age and treatment.	
Comparison groups	Part 1: Alteplase low dose v Part 1: Standard of Care
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29
upper limit	19.2

Secondary: Number of oxygen-free days up to Day 28

End point title	Number of oxygen-free days up to Day 28[11]
End point description:	
Number of oxygen-free days (OFD) up to Day 28. Oxygen-free is defined as free from assistance from oxygen support. The number of oxygen-free days starts from when the patient has a 'lasting' value on	

the WHO clinical progression scale of ≤ 4 and ends on Day 28. A lasting value of ≤ 4 means that the value cannot exceed 4 at a later timepoint. If the patient is liberated from oxygen on Day x, then the number of OFDs is 28-x. If a patient has withdrawn consent prior to day 28 then he will have a missing value for OFD. In any case, if the status of the patient at Day 28 is death, as determined from the vital status page then the OFD=0.

Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint. The endpoint was only planned for subjects in Part 2.

End point type	Secondary

End point timeframe:

Up to 28 days.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint only analyzed part 2 subjects.

End point values	Part 2: Alteplase high dose - NIV patients	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients	Part 2: Standard of Care - IMV patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	8	12	5
Units: Days				
median (inter-quartile range (Q1-Q3))	7.0 (0.0 to 20.0)	4.5 (0.0 to 12.5)	0.0 (0.0 to 5.5)	0.0 (0.0 to 13.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Length of hospital stay up to Day 28

End point title	Length of hospital stay up to Day 28[12]

End point description:

Length of hospital stay up to day 28 was determined based upon the first hospital discharge date, or discharge to another care facility. If the patient died within the first 28 day period, then length of hospital stay was 28.

Full Analysis Set (FAS) consisted of all randomised patients with at least one baseline and one post baseline assessment relating to the primary endpoint. The endpoint was only planned for subjects in Part 2.

End point type	Secondary

End point timeframe:

Up to 28 days.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint only analyzed part 2 subjects.

End point values	Part 2: Alteplase high dose - NIV patients	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients	Part 2: Standard of Care - IMV patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	8	12	5
Units: Days				
median (inter-quartile range (Q1-Q3))	28.0 (16.0 to 28.0)	24.0 (17.0 to 28.0)	28.0 (26.0 to 28.0)	28.0 (16.0 to 28.0)

Statistical analyses

Statistical analysis title	Statistical analysis 21

Statistical analysis description:

Unadjusted mean difference: A restricted maximum likelihood (REML) based Analysis of Covariance (ANCOVA) was used. Adjustment was made for treatment.

Comparison groups	Part 2: Alteplase high dose - NIV patients v Part 2: Standard of Care - NIV patients
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.9856
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	7.6
Variability estimate	Standard error of the mean
Dispersion value	3.6

Notes:

[13] - Calculated as alteplase dose group - standard of care alone.

Statistical analysis title	Statistical analysis 22

Statistical analysis description:

Adjusted mean difference: A restricted maximum likelihood (REML) based Analysis of Covariance (ANCOVA) was used. Adjustment was made for treatment, the number of days under NIV support, baseline D-Dimer level and age.

Comparison groups	Part 2: Alteplase high dose - NIV patients v Part 2: Standard of Care - NIV patients
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.8729
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	7.3
Variability estimate	Standard error of the mean
Dispersion value	3.8

Notes:

[14] - Calculated as alteplase dose group - standard of care alone.

Secondary: Worst PaO2/FiO2 ratio change from baseline to Day 6

End point title	Worst PaO2/FiO2 ratio change from baseline to Day 6[15]

End point description:

Worst PaO2/FiO2 ratio (or inferred PaO2/FiO2 ratio from SpO2) change from baseline to day 6. This assessment was planned to be measured on each of days 0 to 6. but only whilst the patients was still in hospital. The worst (lowest) daily measurement will be used and the higher the value the better the health status of the patient.

- If the patient was still in hospital during day 6 then the day 6 value was used
- If the patient was discharged from hospital prior to day 6 then the value at the time of hospital discharge was used
- If the patient died prior to day 6 then the last value prior to death was used
- If day 6 value was missing but Day 5 value available, the day 5 value was used
- If day 6 value was missing, no Day 5 value available, but day 7 available, then day 7 value was used
- Otherwise value was set to missing for that patient.

Based upon this, the change from baseline for each patient was calculated and used for the analysis.

FAS

End point type	Secondary

End point timeframe:

Up to 7 days.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint only analyzed part 2 subjects.

End point values	Part 2: Alteplase high dose - NIV patients	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients	Part 2: Standard of Care - IMV patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	8	12	5
Units: PaO2/FiO2 ratio				
arithmetic mean (standard error)	70.8 (± 20.7)	0.0 (± 29.2)	-10.9 (± 13.1)	3.4 (± 20.2)

Statistical analyses

Statistical analysis title	Statistical analysis 24

Statistical analysis description:

Adjusted mean difference: A restricted maximum likelihood (REML) based Analysis of Covariance (ANCOVA) was used. Adjustment was made for treatment, the number of days under NIV support, baseline D-Dimer level, baseline PaO2/FiO2 ratio and age.

Comparison groups	Part 2: Alteplase high dose - NIV patients v Part 2: Standard of Care - NIV patients

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0362
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	87.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.3
upper limit	168
Variability estimate	Standard error of the mean
Dispersion value	38.5

Statistical analysis title	Statistical analysis 23

Statistical analysis description:

Unadjusted mean difference: A restricted maximum likelihood (REML) based Analysis of Covariance (ANCOVA) was used. Adjustment was made for treatment.

Comparison groups	Part 2: Alteplase high dose - NIV patients v Part 2: Standard of Care - NIV patients
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0603
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	70.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	145.1
Variability estimate	Standard error of the mean
Dispersion value	35.8

Adverse events information

Timeframe for reporting adverse events:

treated set (TS) including all patients who were randomised and for the alteplase groups, treated with at least one dose.

Adverse event reporting additional description:

Treated Set (TS), included all patients who were randomised and, for patients in the alteplase groups, treated with at least one dose of trial drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Part 1: Alteplase low dose

Reporting group description:

0.3 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.02 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.3 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.

Reporting group title	Part 1: Alteplase high dose

Reporting group description:

0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement.

Reporting group title	Part 1: Standard of Care

Reporting group description:

Standard of Care included best possible treatment regimen established locally and was in line with current guidelines for Acute respiratory distress syndrome treatment.

Reporting group title	Part 2: Standard of Care - IMV patients

Reporting group description:

invasive mechanical ventilation (IMV) patients received Standard of Care, which included best possible treatment regimen established locally and was in line with current guidelines for Acute respiratory distress syndrome treatment. Invasive mechanical ventilation (IMV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 7, 8 or 9.

Reporting group title	Part 2: Standard of Care - NIV patients

Reporting group description:

Non-invasive mechanical ventilation (NIV) patients received Standard of Care, which included best possible treatment regimen established locally and were in line with current guidelines for Acute respiratory distress syndrome treatment. Non-invasive mechanical ventilation (NIV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 6.

Reporting group title	Part 2: Alteplase high dose - IMV patients

Reporting group description:

Invasive mechanical ventilation (IMV) patients received 0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement. Invasive mechanical ventilation (IMV) patients are those with a baseline World Health Organization (WHO) Clinical Progression Scale value of 7, 8 or 9.

Reporting group title	Part 2: Alteplase high dose - NIV patients

Reporting group description:

Non-invasive mechanical ventilation (NIV) patients received 0.6 milligram/kilogram (mg/kg) over 2 hours (Day 1) immediately followed by daily infusion of 0.04 mg/kg/hour over 12 hours (starting on Day 1 and up to Day 5), plus Standard of Care (SOC). One optional additional infusion of 0.6 mg/kg over 2 hours could be given once on Days 2 to 5 in case of clinical worsening, per investigator judgement. Non-invasive mechanical ventilation (NIV) patients are those with a baseline World Health Organization

Serious adverse events	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)	10 / 20 (50.00%)	12 / 22 (54.55%)
number of deaths (all causes)	6	6	9
number of deaths resulting from adverse events	1	0	0
Injury, poisoning and procedural complications			
Subcutaneous haematoma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasoplegia syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 22 (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
Traumatic lung injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haematoma			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute right ventricular failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 22 (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
Cardiogenic shock			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ischaemic stroke			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Vessel puncture site haematoma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Puncture site haemorrhage			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mouth haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic infarction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatic failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	3 / 20 (15.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemoptysis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 22 (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
Pneumothorax			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 20 (10.00%)	3 / 20 (15.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 2	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 22 (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
Respiratory failure			

subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	6 / 22 (27.27%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Renal and urinary disorders			
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 22 (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
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia aspiration			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related bacteraemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 22 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	4 / 22 (18.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Standard of Care - IMV patients	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	4 / 8 (50.00%)	9 / 12 (75.00%)
number of deaths (all causes)	2	3	3
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Subcutaneous haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasoplegia syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic lung injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal haemorrhage			

subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Acute right ventricular failure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Myocardial injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			

subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Ischaemic stroke			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 12 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
General disorders and administration site conditions			
Catheter site haemorrhage			

subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Vessel puncture site haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Puncture site haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mouth haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Gingival bleeding			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic infarction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Acute hepatic failure			

subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Lung disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Pharyngeal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Renal and urinary disorders			
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Haematuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Rhabdomyolysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Device related bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			

subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Septic shock			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Alteplase high dose - NIV patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 17 (41.18%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Subcutaneous haematoma			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vasoplegia syndrome			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic lung injury			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tracheal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Cardiac arrest			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute right ventricular failure			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial injury			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Disseminated intravascular coagulation				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Splenic infarction				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Catheter site haemorrhage				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vessel puncture site haematoma				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Puncture site haemorrhage				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Mouth haemorrhage				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				

subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gingival bleeding				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic infarction				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute hepatic failure				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Epistaxis				
subjects affected / exposed	3 / 17 (17.65%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Lung disorder				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngeal haemorrhage				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumomediastinum				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Urinary bladder haemorrhage				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				

subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Rhabdomyolysis				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacteraemia				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 17 (11.76%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Escherichia bacteraemia				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related bacteraemia				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia staphylococcal				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia pneumococcal				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part 1: Alteplase low dose	Part 1: Alteplase high dose	Part 1: Standard of Care
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)	11 / 20 (55.00%)	12 / 22 (54.55%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	2 / 22 (9.09%)
occurrences (all)	2	0	2
Haematoma			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Hypotension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	1 / 22 (4.55%)
occurrences (all)	0	1	1
Jugular vein thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Administration site haematoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Catheter site haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Chest pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Disease progression			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences (all)	3	0	1

Hyperthermia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Mucosal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	2 / 22 (9.09%)
occurrences (all)	1	0	2
Oedema peripheral			
subjects affected / exposed	2 / 20 (10.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Oedema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Acute respiratory failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Respiratory acidosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Pneumomediastinum			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Lung disorder			

subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	2 / 22 (9.09%)
occurrences (all)	0	1	2
Hiccups			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 20 (0.00%)	5 / 20 (25.00%)	0 / 22 (0.00%)
occurrences (all)	0	6	0
Respiratory failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Respiratory distress			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Agitation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Aggression			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Glomerular filtration rate increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Right ventricular failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Bradycardia			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 20 (10.00%)	3 / 20 (15.00%)	1 / 22 (4.55%)
occurrences (all)	2	3	1
Faecaloma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Gingival bleeding			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Mouth haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	3
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Biliary dilatation			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Decubitus ulcer			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Haemorrhage urinary tract			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Renal failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Renal impairment			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Enterobacter infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Aspergillus infection			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Pneumonia streptococcal			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Pneumonia serratia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Pneumonia bacterial			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Staphylococcal infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Oral herpes			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Neisseria infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Enterococcal bacteraemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	4 / 22 (18.18%)
occurrences (all)	1	2	5
Stenotrophomonas infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Tracheobronchitis			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Vulvitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Hypocalcaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Hyperlactacidaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Hyperkalaemia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	2 / 22 (9.09%)
occurrences (all)	2	0	2
Metabolic alkalosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Cell death			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	3 / 22 (13.64%)
occurrences (all)	1	2	3
Hypophosphataemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1

Hyperglycaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	3 / 22 (13.64%)
occurrences (all)	1	0	3

Non-serious adverse events	Part 2: Standard of Care - IMV patients	Part 2: Standard of Care - NIV patients	Part 2: Alteplase high dose - IMV patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	4 / 8 (50.00%)	11 / 12 (91.67%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 5 (40.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Jugular vein thrombosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Administration site haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Catheter site haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Disease progression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hyperthermia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1

Mucosal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Acute respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory acidosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pneumomediastinum			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Lung disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hiccups			

subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory distress			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Agitation			
subjects affected / exposed	0 / 5 (0.00%)	2 / 8 (25.00%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Aggression			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Fibrin D dimer increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Glomerular filtration rate increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Atrial fibrillation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Right ventricular failure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Bradycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 5 (40.00%)	0 / 8 (0.00%)	3 / 12 (25.00%)
occurrences (all)	2	0	3
Faecaloma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gingival bleeding			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Mouth haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Biliary dilatation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Subcutaneous emphysema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Decubitus ulcer			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Haemorrhage urinary tract			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Renal impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Enterobacter infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Aspergillus infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pneumonia streptococcal			

subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pneumonia staphylococcal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pneumonia serratia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pneumonia bacterial			
subjects affected / exposed	1 / 5 (20.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Staphylococcal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Neisseria infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Klebsiella bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Enterococcal bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Stenotrophomonas infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tracheobronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Urinary tract infection			

subjects affected / exposed	0 / 5 (0.00%)	2 / 8 (25.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Vulvitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypernatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyperlactacidaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 8 (12.50%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Metabolic alkalosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Cell death			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 2: Alteplase high dose - NIV patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 17 (70.59%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Haematoma			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Jugular vein thrombosis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Administration site haematoma			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Catheter site haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Disease progression			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hyperthermia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Mucosal haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Acute respiratory failure			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Respiratory acidosis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Pneumomediastinum			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Lung disorder			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Haemoptysis			

subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Respiratory failure			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Respiratory distress			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Agitation			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Aggression			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Fibrin D dimer increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all) Glomerular filtration rate increased subjects affected / exposed occurrences (all) Haemoglobin decreased subjects affected / exposed occurrences (all) Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0		
Injury, poisoning and procedural complications Overdose subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all) Atrial fibrillation subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all) Right ventricular failure subjects affected / exposed occurrences (all) Bradycardia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Faecaloma			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Gingival bleeding			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Mouth haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Biliary dilatation			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Decubitus ulcer			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Haemorrhage urinary tract			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Renal impairment			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Infections and infestations			
Enterobacter infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Candida infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Aspergillus infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pneumonia streptococcal			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Pneumonia staphylococcal			

subjects affected / exposed	0 / 17 (0.00%)			
occurrences (all)	0			
Pneumonia serratia				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences (all)	0			
Pneumonia bacterial				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Staphylococcal infection				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences (all)	0			
Oral herpes				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences (all)	0			
Neisseria infection				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences (all)	0			
Klebsiella bacteraemia				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences (all)	0			
Enterococcal bacteraemia				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	3 / 17 (17.65%)			
occurrences (all)	3			
Stenotrophomonas infection				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences (all)	0			
Tracheobronchitis				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences (all)	0			
Urinary tract infection				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences (all)	0			
Vulvitis				

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0		
Hypocalcaemia subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		
Hypernatraemia subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0		
Hyperlactacidaemia subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0		
Hyperkalaemia subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		
Metabolic alkalosis subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0		
Cell death subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0		
Hypokalaemia subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		
Hypophosphataemia subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0		
Hyperglycaemia subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2020	- Vital signs and laboratory tests at Day 6 were added. - Details on vital signs assessments and laboratory samples needed for APACHE II and Sequential organ failure assessment (SOFA) score calculations were added: if a patient was discharged from hospital prematurely, last evaluation during hospital stay was expected on day of discharge. - Effect on D-Dimer and fibrinogen was added as a risk associated with alteplase to increase safety and provide guidance for physicians for changes in coagulation system. - Serious adverse events, and non-serious adverse events which were relevant for the reported Serious Adverse Events (SAE) were to be reported on the BI SAE form and sent via fax. Exception was added for Russia and United Kingdom, where SAE form was to be sent via Clinergize. - Method for blood withdrawal for quantification of analyte plasma concentrations was changed from indwelling venous catheter or venepuncture to single-time venepuncture. - SOFA score table was replaced with new one and reference to calculator for SOFA score removed to ensure unique score calculation as referenced.
05 October 2021	- Key-secondary endpoints - Secondary endpoints - Number of patients in Part 2 updated / planned number of patients on NIV/ IMV updated - Randomisation additionally stratified by D-dimer status - Alteplase labelled to alteplase dosing regimen B - Updated Inclusion/Exclusion criteria - Treatment duration update
17 February 2022	Stratification for randomisation changed from 'D-dimer levels (≥3-fold to <5-fold ULN, versus ≥5-fold ULN)' updated to 'D-dimer levels (≥ULN to <5-fold ULN, versus ≥5-fold ULN)'.

Notes:

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.

Results for the IMV patients were only analyzed descriptively due to insufficient enrolled patients.
For all-cause mortality, the NIV arm did not have enough events to perform the adjusted model, instead the unadjusted model is presented.

Notes: